18

CYCLOPÆDIA

OF THE

PRACTICE OF MEDICINE.

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VOL. XVII.

GENERAL ANOMALIES OF NUTRITION,

AND

POISONS.

BY

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Translated by

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ALBERT H. BUCK, M.D., NEW YORK,
EDITOR OF AMERICAN EDITION.

NEW YORK:
WILLIAM WOOD AND COMPANY,
27 GREAT JONES STREET.
1878.

TROW'S PRINTING AND BOOKBINDING COMPANY,
205 *to* 213 *East Twelfth Street,*
NEW YORK.

BIOGRAPHICAL SKETCHES OF THE AUTHORS.

BERNHARD NAUNYN was born in Berlin on the second day of September, 1839, and received his education partly in that city, partly in Bonn. While a student, his duties as an amanuensis, first of Prof. Reichert, afterwards of Prof. Frerichs, afforded him an early opportunity of familiarizing himself with both anatomy and internal medicine. From 1863 to 1868 he was an assistant in the Medical Clinic at Berlin (service of Prof. Frerichs). In 1869 he was invited to fill the position of Professor of the Medical Clinic at Dorpat. In 1871 he was called to fill the same position in Berne, Switzerland. Finally in 1872 he accepted a similar call from the University of Königsberg, in Prussia.

Naunyn's first published works related to questions of anatomy. Thus, his doctorial thesis was "On the Development of the Echinococcus," and in 1866 he published a paper "On the Development of Cancers of the Liver." Since 1863, when he became an assistant in Frerichs' Clinic, his chief interest has centred in questions of physiological chemistry and experimental pathology. In the former department he has published the following papers: "On the Chemistry of Transudations and Pus;" "On the Behavior of Carburetted Hydrogen in the Organism." In the department of general pathology, he has made exhaustive studies on the subjects of Icterus, Fever, and Diabetes. Upon the first-named topic he has written two papers, while upon the second he has written four, two of which, however, were published as coming from him and Quincke conjointly ("On the Influence of the Central Nervous System upon the Generation of Heat"), and one from him and Dobrzansky conjointly ("Contribution to the Theory of Rise of Temperature in Fever"). All three of these were published in 1873. In a paper written by him in 1875 on Diabetes ("Contribution to the Theory of Diabetes Mellitus"), Naunyn has incorporated not only the results of his own investigations upon this question, but also those of his pupils. Finally, two other works remain still to be mentioned, *viz.*, one published by Francken and himself in 1873, "On the Coagulation of Blood in the Living Animal," and a second by Eichhorst and himself in 1874, "On Degeneration and Regeneration of the Spinal Cord."

The articles which he published before 1873 will all be found in the Archives of Reichert and Dubois, while the later ones have appeared in the "Archiv für Experimentelle Pathologie, etc.," published by Klebs and Schmiedeberg in conjunction with Naunyn.

Rudolf Boehm, the oldest son of the late Dr. Martin Boehm, was born in Nördlingen, Bavaria, on the 19th of May, 1844. After completing his studies at the gymnasium, he visited first the University of Munich, then that of Würzburg, in which latter he took the degree of doctor during the summer of 1867. His university studies were interrupted in 1866 by the outbreak of the war, and for a time he served as an assistant surgeon in the military hospital at Munich. From the winter of 1866 to the spring of 1868 Boehm devoted his time chiefly, under the direction of F. von Recklinghausen, to pathological and pathologico-anatomical researches, the results of which are incorporated in the following publications, which are his maiden efforts: "Contribution to the Normal and Pathological Anatomy of the Joints" (Dissertation. Würzburg, 1868); "Experimental Studies on the Dura Mater of Man and of Mammals" (Virchow's Archiv. Bd. 47. p. 218 ff.).

In the spring of 1868 Boehm was appointed an assistant in the Psychiatric Clinic of the Julius Hospital in Würzburg, and served in this capacity till the spring of 1870. The duties of this position gave him ample opportunities of becoming familiar with practical medicine, for in addition to his labors in the wards of the insane, he was obliged to prescribe for the patients in the very large department devoted to epileptics, and also in the so-called "Pfründe." It was during this period that he published a German edition of Maudsley's "Physiology and Pathology of the Mind" (Würzburg: Stnber, 1870).

In the spring of 1870, after completing his service in the Julius Hospital, Boehm went to Leipzig in order to continue his researches in experimental physiology under the direction of Prof. Ludwig. Already in the following summer, however, the breaking out of the Franco-Prussian war compelled him to abandon his scientific studies. He took part in the campaign as battalion surgeon of Bavarian troops, and did not resume his work in Leipzig until April, 1871. In the following autumn he established himself as a "Privatdocent" in the University of Würzburg, his "Habilitation" thesis being entitled "Studies on Heart-Poisons" (Würzburg: Stuber, 1871). He began to deliver lectures during the winter semester of 1871–72, and at the same time acted in the capacity of assistant to Prof. A. Fick, in the Physiological Institute of the Würzburger Hochschule. The following articles were published by him during this period: "Experimental Investigations on the Effects of Digitalis and Digitalin" (Pflüger's Archiv, Bd. V.); (conjointly with A. Hartmann, of Geneva) "Investigations on the Physiological Effects of the German Aconitin" (Verhandlungen der Würzburger medicinisch-physikalischen Gesellschaft, 1872); "On the Influence of Arsenic Acid on the Unformed Ferments" (Ibid.), etc.

In the summer of 1872 Boehm was called to the University of Dorpat, to fill the chair of Materia Medica, Dietetics, and History of Medicine, which had been left vacant by Prof. Schmiedeberg. He accepted the call, and in the following autumn moved to Dorpat, where he has remained up to the present time. As Director of the Pharmacological Institute of the Dorpater Hochschule, Boehm has published in the Archiv für experimentelle Pathologie und Pharmakologie the following experimental pharmacodynamic and toxicological articles, based either upon

his own researches or upon those which his pupils have carried out under his direction:

1. On the Effects of Pseudaconitin (Nepalin). Archiv für exper. Path. und Pharm. Bd. I. 1872.

2. On the Effects of Arsenic Acid. Ibidem. Bd. II. 1873.

3. On the Influence of Arsenic Acid upon Yeast Fermentation, etc. Ibid. II. 1873.

4. On Nativelle's Preparations of Digitalis. Ibid. II. 1873.

5. On the Effects of Prussic Acid, etc. Ibid. III. 1874.

6. On the Effects of the Salts of Ammonia. Ibid. IV. 1874.

7. On the Effects of the Salts of Baryta. Ibid. V. 1875.

8. On the Nervus Accelerator Cordis of the Cat. Ibid. V. 1875.

9. On Paradoxical Effects produced by the Vagus; a Contribution to the Knowledge of the Effects of Curare. Ibid. V. 1875.

10. On the Poisonous Constituent of the Water-Hemlock (Cicuta Virosa) and its Effects. Ibid. VI. 1876.

11. Contribution to the Pharmacology and Toxicology of the Preparations of Iodine. Ibid. VI. 1876.

12. The Poisonous Alkaloids of the Seeds of Stavesacre (Delphinium Staphysagria). Ibid. VI. 1876.

13. On Restoration to Life after Poisonings and after Asphyxia. Ibid. 1877.

Recently Boehm has published, conjointly with the clinicist F. A. Hoffmann, "Contributions to the Physiology of the Changes which Carburetted Hydrogen undergoes" (Archiv für exp. Pathol. Bd. VIII. 1878).

Hermann von Boeck was born on the fourteenth of August, 1843, in a small village of the Bavarian district of Allgau. His father was the practising physician of the place. At the age of ten, von Boeck was sent from home to a school in Bregenz, on the Lake of Constance. In 1855 he entered the St. Stephen's Gymnasium in Augsburg, and in 1860 the Gymnasium of Munich, where in 1863 he completed his preliminary education. During the following three years he pursued his medical studies at the University of Munich. When the war broke out in 1866, he entered the army as an assistant surgeon, and served in the campaign against the Prussians. Upon the termination of the war in the autumn of 1866, he was appoined an assistant of Prof. von Lindwurm, in the Munich Hospital, and served in this capacity till the early part of 1870. In 1868 and 1869 he passed both the university and the State examinations. In 1870 he continued his studies in Berlin and in Vienna, and in the autumn of the same year began the practice of medicine in Munich. In 1871 he established himself in the university as a "Privatdocent" in Pharmacology. In 1876 he was appointed "Extraordinary Professor" of Materia Medica, Toxicology, etc.—a position which he still holds.

Von Boeck's principal literary works are the following:

"On the Cold Water Treatment of Typhus." Bayer. aerztliches Intelligenzblatt. 1870.

"Investigations on the Decomposition of Albumen in the Human Being under the Influence of Mercury and Iodine." Munich, 1869. Zeitschrift für Biologie, von Pettenkofer, Voit, et al. 8. p. 17.

"Investigations on the Manner in which Albumen becomes decomposed in the Bodies of Animals under the Influence of Morphine, Quinine, and Arsenic Acid." Munich, 1871. M. Rieger'sche Buchhandlung. 8. p. 52.

"Investigations on the Interchange of Gases in the Bodies of Animals under the Influence of certain Remedies." Zeitschrift für Biologie. 1875.

"On the Effects of Arsenic upon the Tissue-Changes." Zeitschrift für Biologie. 1876; and Centralblatt für die medicinischen Wissenschaften von Rosenthal and Senator. 1877.

EDITOR'S NOTE.

In the Table of Contents of volume XVI., Dr. E. Buchanan Baxter is credited with the translation of the chapters on Anæmia, Chlorosis, Progressive Pernicious Anæmia, and Corpulence. The translation of the latter chapter, however, should have been credited to Dr. John Todhunter, of Dublin.

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Historical Introduction.

The earliest historical mention of true cases of the hemorrhagic diathesis, which correspond in their habitual and at the same time hereditary character to the "hæmophilia" of the present day, is in all probability to be found in a passage in the writings of the Arabian physician, Khalaf Abul Kasim el Zahrewi, known also as Abul Kasim or Alsaharavi, who died at Cordova in A.D. 1107. Although this writer had no knowledge of the affection except what was told him by individuals who were afflicted with the idiosyncrasy, his description is so true in its main outlines to what we now know as the bleeder disease, that one cannot but recognize his account as the first authentic evi-

dence of the existence of the affection in earlier times, and we therefore give the passage in full as it appears in the barbarous Latin translation by Paulus Ricius (l. c.):

De passione fluxus sanguinis a quocumque locorum.

"Vidi in quibusdam regionibus casale quoddam, dictum 'al-kiria,' viros, qui narraverunt mihi, quoniam, cum accidit in corporibus ipsorum vulnus aliquod magnum, indesinenter fluit sanguis ex vulnere, quousque moritur. Et recitaverunt mihi super hoc, quod quibusdam ex pueris suis, cum fricaret manu gingivas, cepit sanguis fluere ex illis, donec mortuus sit. Alius vero, flebotomatus a minutore sanguinis, non cessavit ex eo fluere, donec periit. Et universaliter eorum mors, ut in pluribus, contigit in hunc modum. Haec est res, quam nunquam et nusquam vidi, nisi in casale praedicto, nec reperii hoc accidens ab aliquo antiquorum memorantium, nec scio ejus causâm, et, quod mihi videtur de curatione ejus, est, quod ille, cui hoc accidit, celeriter cauterizet locum, donec sanguis restringatur, et ego minime probavi hoc, et est apud me monstrum."

The above quotation evidently refers to the existence of a disposition in the males of certain families to obstinate and uncontrollable hemorrhages after the reception of injuries—a disposition quite analogous to that observed in the "bleeders" or "hæmophilists" of our own day. That Alsaharavi was correct in his assertion that none of the older writers had referred to the disease, is shown by the entire failure of modern research to discover any trace of the affection in the works of the Greek, Latin, Arabian, or other ancient authors. Furthermore, in characterizing finally the extraordinary behavior of the individuals in question as something "monstrous," Alsaharavi manifests a feeling from which even more recent times have found it difficult to escape. For, previous to the rediscovery of hæmophilia as a special form of disease about a century ago, a long period elapsed during which persons who were afflicted with this idiosyncrasy would naturally have been looked upon as subjects of "demoniac possession;" indeed, as Grandidier has well pointed out, it must be regarded as a really fortunate circumstance that hæmophilia was in fact almost unknown among the populations of Europe during the entire interval from Alsaharavi (1107) to Fordyce (1784), because otherwise the affection could scarcely have failed to play a very dangerous part in the history of civilization during the times of witchcraft and the persecutions attending this delusion.

The symptoms of hæmophilia are of such a striking character that it is difficult to explain the almost complete gap in the history of the disease during the latter part of the middle ages, and even in modern times up to the beginning of the eighteenth century, except upon the supposition that cases of this affection were comparatively rare during the whole of this long period. That cases did occur, however, from time to time, is not only intrinsically probable, but is shown by reports of isolated cases, although some of these accounts are not so complete as might be desired.

Thus, Alexander Benedictus, who died in 1525 while professor at Padua, gives an account of the singular death of a Venetian barber, who, while clipping the hairs at the end of his nose, accidentally punctured the skin with the point of the scissors, and died from the hemorrhage thus produced (l. c.). The passage in question unfortunately does not give us any further information, and is, moreover, somewhat obscurely worded; but it is difficult in reading it to avoid the suspicion that it really refers to a case of hæmophilia. Far more trustworthy is the report of another case, discovered by Virchow in the almost forgotten work of Philipp Hoechstetter (l. c.), a practising and hospital physician in Augsburg, who died in 1635; the case was republished by Virchow (1863) in his Archives (Vol. XXVIII., p. 426). The patient was a boy, who from birth had suffered on all possible occasions from more or less severe attacks of bleeding, such as umbilical hemorrhages during the first days of life, repeated epistaxes, bloody stools and petechial eruptions, and in fact presented in every respect a very well-marked picture of hæmophilia. Still another case, reported by Dr. Banyer[1] as early as 1743 in England, has recently (1872) been discovered by Wickham Legg, after having been entirely overlooked for more than a century. The patient, a young man twenty-four years of age, was attacked for the first time in 1729 with a dangerous hemorrhage, after a slight puncture from a rusty nail in the sole of the right foot, and thereafter, up to the time of his death in 1738, continued to

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[1] Philosophical Transactions, Vol. XLII. 1743. No. 471, p. 268.

manifest a marked tendency to hemorrhages of the character of hæmophilia upon a great variety of occasions.

With the exception, however, of these few older reports, our knowledge of hæmophilia as a specific form of the hemorrhagic diseases is entirely an acquisition of modern times; in fact, it cannot be truly said to have commenced until the present century. To be sure, towards the close of the last century Fordyce (1784) gave an account of a hemorrhagic disposition noticed by him in several individuals belonging to the same family circle—the disposition being therefore probably of an hereditary character; and soon afterwards other families of bleeders were reported in Germany (Westphalia) by a writer in the "Medicinischen Ephemeriden," published at Chemnitz (1793), and by Rave (1798). Still, for some years these articles attracted but little attention, and no general interest was excited in Europe until after a series of cases had been reported in American journals. The first of these American articles appeared in the Medical Repository of New York, and contained an account by Otto of a widespread bleeder family, in which the disease could be traced back for nearly a hundred years. Three other bleeder families are referred to, observed by Rush and Boardley. The word "bleeder" was here first used. This epoch-making article was soon followed by others: one by Coxe and Smith[1] (1805), another by Hay (1813) of the large bleeder family Appleton-Brown, and finally, in 1817, another report of a bleeder family by Buel. These cases, in addition to those reported by Fordyce and his immediate German successors, and some other observations published by Consbruch (l. c.) in 1810, now afforded for the first time sufficient material for a systematic description of the disease.

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[1] This article consists of a letter written by Dr. E. H. Smith, of New York, in 1794, to Dr. Rush, of the same city, in reference to the case of a child who died from hemorrhage, which had previously recurred a few days before each birthday, and had always stopped upon the birthday. Death occurred five days before his fourth birthday. The case has always been quoted by the Germans as Coxe's or Lowthorp's; but, as Wickham Legg has pointed out in his work on Hæmophilia (London, 1872, p. 20), Coxe's only connection with the case was an addendum to the letter, quoting two other instances from Lowthorp's Abridgement of the Philosophical Transactions of London, neither of which cases, however, seems to have been an instance of the genuine disease.—TRANSLATOR'S NOTE.

This task was undertaken by Nasse, and, considering the imperfect material at his command, his treatment of the subject cannot be too highly praised. In an article published in 1820 (l. c.), on "An hereditary disposition to fatal hemorrhages," he quotes all the cases which had been reported since the time of Alsaharavi, and discusses the etiology, symptoms, and terminations of the bleeder disease with the same thorough method and classic clearness of style which characterize all of his writings. The article excited everywhere, but especially in Germany, a lively interest in the study of this interesting affection, and was followed between this time and 1850 by numerous publications, many of them inaugural dissertations written at Würzburg and Berlin under the influence of the teachings of Schoenlein, who was much interested in the disease, and was the first to give it a permanent position in systematic pathology under the present name "hæmophilia" (or hæmorrhophilia). In other countries also, particularly England, North America, and Switzerland, a considerable number of new cases, as well as of families of bleeders, were reported in journal articles and larger treatises; indeed, this period of thirty years surpassed all others, past or present, in the copiousness of its literature on the subject. Among the German articles we may mention, especially, those by Krimer (1820), Elsaesser (1824–1833), Steinmetz (1828), Rieken (1829), Kuhl (1834), and Grandidier (1832–1839); followed in 1849 by the two articles of Wachsmuth and Lange, which were the most important and comprehensive that appeared during this period; and in 1851 by the valuable reports of Meinel and Martin, in reference to bleeder families in Franconia and Thuringia. Wachsmuth's article is a true monograph of the disease. It not only shows an intimate acquaintance with the previous literature of the subject, but contains also an account of several cases in his own family circle, and is the best and most complete treatise, with the exception of the earlier article of Nasse and the later ones of Virchow, Grandidier, and Legg; while to Lange we are indebted for the first vigorous prosecution of the statistics of the disease — a branch of the subject attended by immense difficulties.

Of the articles which appeared in other countries during this period, the most valuable are those of the American physicians,

Reynell Coates, Hughes, and Bowditch (ll. cc.); in England, the treatises of Blagden, Davis, Murray, Osborne, Kendrick, Lane, Cochrane, Allan, and Clay (ll. cc.); and in Switzerland, Vieli's interesting reports of the two large bleeder families at Tenna, in Graubünden, to which we shall have repeated occasion to refer in the present article.

The comparative scantiness of the literature on this subject in France, and other countries speaking the Romanic languages, is mainly due to the lack of interest occasioned by the rarity of the disease among the populations of the so-called Latin race. Several important articles, however, by French writers (Roux, Lafargue, Lebert, Dequevauviller, Dubois, etc.), will be found mentioned in the preceding bibliography.

Among the more extended articles since 1850, one of the most valuable is the chapter devoted to this affection in Virchow's Manual of Special Pathology (1854, Vol. I. p. 263 et seq.). Brief as it is, this excellent article contains everything of importance on the subject up to that time, and by its clear statement of the causes of the disease, and careful description of its chief symptoms, gives a true and vivid picture of the affection. In the following year (1855) appeared an exhaustive monograph by Grandidier, who, as we have seen, had already published several shorter communications, and had done good work in promoting the study of the subject by his digests of current literature on hæmophilia in Schmidt's Jahrbücher des gesammten Medicin.[1] To these treatises of Grandidier, Virchow, Wachsmuth, and Nasse, more than to any others, we are mainly indebted for our present knowledge, and we shall, therefore, use them freely in our own account of the disease, at the same time urgently recommending the reader to consult the articles themselves to supply any deficiencies that may appear here.

Of recent publications in other countries, Wickham Legg's work (London, 1872) requires particular mention. It contains several new cases observed by the author, reviews thoroughly the entire previous literature of the disease, and advances some

[1] 1862, Vol. CXVII. p. 329; and 1872, Vol. CLIV. p. 81.

original opinions characterized by a soundness of judgment which entitles them to careful consideration.

The preceding summary must suffice, as it is not the object of this historical introduction to enter fully into the details of the literature of hæmophilia. Nor is it desirable to detain the reader with an account of all the theories which have been advanced in explanation of the anomaly since the affection came to be more generally known nearly a century ago. It is only necessary to say that none of them has gained exclusive acceptance, and that this fatal affection still remains one of the "enigmas" of pathology, the solution of which must be left to the future.

A few words may be added, however, with respect to the *temporal* and *spatial frequency* of the disease. That the affection has gained in frequency to an important degree within a comparatively recent period can scarcely be doubted. As we have already seen, not a trace of hæmophilia is to be found anywhere in the entire literature of the middle ages and earlier part of modern times, with the exception of the doubtful passage in Alexander Benedictus, and Hoechstetter's case; and in none of the bleeder families can the disease be followed back further than the beginning of the last century. To be sure, this silence of writers during the period referred to does not necessarily indicate the *entire* absence of the disease in those times; still, as suggested above, some mention of it might naturally be expected if the affection had been *frequently* observed. Moreover, in consequence of the great fecundity of bleeder families, and the marked inheritability of the anomaly, there seems to be every likelihood that the affection will become still more common in the future. The few bleeders existing two hundred years ago have probably by this time a considerable number of bleeder descendants, and this number is likely to steadily increase. Certainly thus far the natural restrictions to the propagation of the disease—the premature death of many members of these families, and the failure of others to beget offspring after attaining the proper age—have failed to check the progress of the affection, not to mention the possibility of its spontaneous extinction. It becomes a question, therefore, whether active precautions, of both a private and public nature, may not perhaps be warrant-

able to prevent the disease ultimately becoming a social calamity; but the full consideration of this inquiry must be deferred to the chapter on Prophylaxis.

As to the *spatial frequency*, or, in other words, the *geographical extension* of hæmophilia, statistics seem to show that the disease occurs more frequently in certain countries and groups of countries than in others, and is therefore *not uniformly* distributed over the earth's surface. From the more or less uncivilized portions of the globe reports of either the existence or non-existence of the disease are naturally wanting; still, even in countries thoroughly penetrated by the scientific spirit, differences as to the frequency of the affection are noticeable, which cannot be attributed to a negligence of medical observation. Thus, in Germany, where, particularly in the Rhine and Main districts, a special industry in the collection of cases was awakened by Nasse and Schoenlein, the disease still seems to be *exceptionally* common, notwithstanding the interest excited elsewhere. Next to Germany in the order of frequency comes Great Britain, followed by the northern countries Sweden, Norway, and Denmark; then North America, Holland, Belgium, Switzerland, Russia, Poland, and France, while no cases have been reported from Italy, Spain, Portugal, Greece, and Turkey. Upon the whole, therefore, the widespread Anglo-Germanic family of nations in both the Old and New World appears to be affected much more frequently than the populations of the so-called Latin race; but that the latter, and the Slavic nations also, are not wholly exempt, is shown by reports of several cases in France and Russia; and that, finally, the affection is not confined solely to the so-called Caucasian race, appears from a recent lengthy account by Heymann (l. c.) of a Malayan family of bleeders at Palembang, in Java. It is clear, moreover, from the geographical distribution of the disease, that the prevalence of hæmophilia is little or not at all influenced by climatic differences, and the same remark will apply also to the elevation of the regions affected. Cases are reported of bleeders and families of bleeders from the lowlands of Holland and Livland, as well as from the high Alpine valleys of Switzerland (Vieli); in fact, wherever the disease has been observed, it has always presented

the same stereotyped form, whatever the external conditions of geographical position or social life.

We append a table of the geographical distribution of the disease, comprising the cases compiled by Grandidier up to 1872, together with all the new cases which we have discovered for 1873 and 1874. It shows strikingly the unenviable pre-eminence of the Anglo-Germanic race, and particularly of the German nation, in respect to the prevalence of the disease. The table includes 650 authentic cases occurring in 219 families. Of these families there were in

Germany	94
Great Britain	52
North America	23
France	22
Russia and Poland	10
Switzerland	9
Sweden, Norway, and Denmark	6
Holland and Belgium	2
Java	1

General Definition of the Disease.

As commonly observed, *hæmophilia* or the *bleeder disease* (hæmorrhophilia, hemorrhagic idiosyncrasy) may be defined as a *congenital* and *habitual hemorrhagic diathesis*, since the extremely obstinate and dangerous hemorrhages for which bleeders are noted usually begin in the very *earliest* years of life, and recur *habitually*. At all events, it is decidedly exceptional for an *habitual* hemorrhagic tendency, accompanied by the other clinical peculiarities to be presently described, to originate in *middle* life, so as to warrant us in regarding the disposition as *acquired*. On the other hand, it is equally uncommon for an individual who has been a marked bleeder in infancy, and in whom therefore the disposition was presumably congenital, to lose the idiosyncrasy completely in early youth, and remain thereafter entirely free from hemorrhagic attacks. In fact, the congenital origin and the habitual nature of the disposition are so constantly observed together in the so-called bleeders, that although each of these attributes is doubtless important by itself, it is unquestionably their combination that constitutes the chief characteristic of hæmophilia.

For the present we may be permitted to rest with this general definition, leaving for future consideration those exceptional cases of hæmophilia in which either the congenital or the habitual character of the affection is but slightly marked or entirely absent. As we shall see later, some of these cases, as well as some even quite *transitory* forms of hemorrhagic diathesis, are clearly entitled by their etiology to be regarded as hæmophilia; still, in such a broadening of our conception of the disease, it is evident that these *anomalous* and *rudimentary* forms must lack those external characters which are pathognomonic of the bleeder anomaly, and that the diagnosis of such cases, therefore, can never be more than *conjectural* (see Diagnosis).

On the other hand, if we confine ourselves to the usual and well-marked forms of the disease, it will be seen that it is just these two attributes which chiefly distinguish hæmophilia from other hemorrhagic affections, particularly *scurvy* and the *morbus maculosus Werlhofii* (see the two following articles). All of these other forms of hemorrhagic diathesis, especially the two mentioned, present neither of these attributes, but are essentially *acquired* and *transitory processes*. Hæmophilia, on the other hand—at least so far as we can judge from clinical symptoms—does not appear to be in any true sense a pathological process or morbid "accident," but rather an abnormal "condition" of the living organism, and probably depends for its material substratum not upon a tissue-change which runs a definite course, but far rather upon an *original structural vice* (vitium primae formationis). Were such an anatomical basis for the disease actually demonstrated in the form of some abnormity, which we could not but regard as really a so-called "defect of organization," our difficulties as to the nature and proper definition of hæmophilia would naturally end at once, and it would only remain to investigate those exceptional conditions under which the manifestations of the anomaly, instead of appearing at the outset and throughout the course of life, occasionally appear only at a later age, or even only transitorily. Unfortunately, however, it must be confessed that our knowledge of the anatomical nature of the bleeder diathesis is as yet little more than rudimen-

tary, and that for this very reason the affection still belongs to the obscure problems of special pathology.

As a strict *definition of the nature* of the bleeder disease is therefore at present impracticable, these few remarks must suffice, little as they really add to our knowledge of the pathological condition which underlies the disease. In the further consideration of our subject, also, the disadvantages of not having a definite established theory of the affection will be equally apparent. Thus, in the following chapters on the causes, general picture, and individual symptoms of the disease, it will be impossible to treat these topics synthetically in a logically connected manner, and we shall therefore be obliged to content ourselves at first with a mere analysis of the facts as they have been ascertained empirically, without attempting any *a priori* explanations either as to the mode of action of the observed causes, or as to the origin of particular symptoms. After these points have been discussed, we shall again take up the question in regard to the nature of the affection—that is, in regard to the internal connection between the clinical facts. The results of investigation, as we have already intimated, certainly afford but a very unsatisfactory answer to the question, and we should be disposed to abstain altogether from any theoretical discussion of the nature and mode of origin of hæmophilia, were it not that the *didactic* character of the present work demands that at least an attempt should be made at a comprehensive deduction of the facts observed. It is this consideration alone, and not the consciousness that we have any exhaustive theory of our own to offer, that has led us to devote a short theoretical excursus to the subject later in the article.

Etiology.

A. *Predisposing Causes.*

1. *Hereditary family disposition.* Of all known predisposing causes of the bleeder disease, this is unquestionably the most striking and important. Grandidier speaks of the affection

as altogether "the most hereditary of all hereditary diseases;" while Nasse, in the very title of his work—"An Hereditary Disposition to Fatal Hemorrhages"—shows the importance he attributed to this characteristic which he was the first to make generally known. In fact, when one case of the disease has occurred in a family, *i. e.*, in a group of blood-relations, other members are almost always affected sooner or later. This cumulation of the affection in certain families becomes readily apparent when we compare the *total* number of recorded cases with the number of *families* affected. Such a comparison shows that the number of individual cases is almost three times as large as the number of families; or, in other words, that hæmophilia, when it once manifests itself in a family circle, is rarely content with a *single* victim.

Grandidier's compilation in 1862 included 512 cases distributed among 174 families. By 1872, according to the same writer, these numbers had increased to 631 and 213 respectively. For the years 1873 and 1874 we have discovered 19 more cases reported in medical literature, occurring in 6 families. This gives a total, therefore, of 650 bleeders to 219 families, or *nearly three bleeders to every family affected.*

This cumulation of the affection in certain families — the so-called bleeder families—sometimes takes place more or less rapidly through the birth of a greater or less number of bleeder children in a family where the parents and ancestors have been entirely free from hæmophilia; at other times the cumulation develops *gradually* through a longer period of time, the anomaly starting in a single individual, and descending directly through a series of successive generations. In the first case we have to deal with what may be termed a *multiple congenital origin of hæmophilia;* in the latter case with a *direct transmission* of the disease. Usually, however, when the first mode of cumulation has once disclosed itself, the other ultimately becomes associated with it, since the occurrence of several congenital cases in a family is generally followed by a direct transmission of the disease. A *third*, and at the same time the *most important* mode of propagation, is by means of what may be called *indirect transmission.* Thus, after one or more cases of hæmophilia have appeared among the children of healthy parents, the

affection is usually handed down, not so much by the bleeders themselves, as by their non-bleeder brothers and sisters; and this singular mode of transmission of the outward manifestations of the disease may be repeated for several generations. In such cases, therefore, if we leave out of account the genealogical starting-point of the affection, the clinical or non-latent phase of the disease is evidently propagated in its further course along side or *indirect* paths, and not in the line of direct descent. Now, while the single congenital origin of hæmophilia in families hitherto free from the disease merely increases the number of individual cases in equal proportion to the number of bleeder families, it is clear that by the much more common modes of propagation—multiple congenital origin, and direct and indirect transmission—the number of individual cases increases much more rapidly than the number of bleeder families, and that there is therefore good reason to apprehend that the present ratio of three to one, instead of remaining constant, will steadily become larger in the future. If it seems surprising, on the other hand, that the present ratio is so small, it should be borne in mind that our exact historical knowledge of hæmophilia dates back only to the end of the last century, and that no careful statistical studies were made until quite recently—in fact, only since the time of Lange. The main cause, however, for this low ratio, doubtless lies in the operation of certain factors, which tend directly to restrict the multiplication of primitive cases, as well as to prevent the cumulation of the disease. The proportion between bleeders and bleeder families must unquestionably, even by this time, have become far larger than it is, if (1) *all new members of a bleeder family were themselves actually bleeders*, and if (2) *all bleeders produced offspring;* but, in point of fact, there are important limitations in both these particulars. Thus, many of the new members of these circles fail to manifest the disease at all, and while some of these failures are apparently mere irregularities of a completely erratic character, others, as we shall see in the following section, are observed so frequently that they may almost be said to follow a law of the disease. On the other hand, a very large number of actual bleeders die from the disease so early in life (see Terminations) as to be unable to take any share in the

propagation of the anomaly. Indeed, this great premature mortality of bleeders is the main reason—aside from another to be considered under the Sexual Disposition—why the direct hereditary transmission of hæmophilia is much more rare than the indirect; since the non-bleeder brothers and sisters, on account of their freedom from this danger to life, far more commonly attain the procreative age.

On the other hand, bleeder families present another peculiarity, which, instead of restricting, tends rather to increase the number of cases in these circles, viz., the *extraordinary fruitfulness* of the non-bleeder brothers and sisters—a peculiarity, moreover, of great importance in relation to the indirect transmission of the disease through these members of the family. Since attention was first called to this remarkable fact by Wachsmuth, the confirmations of it by later observers have become so numerous that it can no longer be regarded as merely accidental. Thus, direct investigation has shown that the average number of legitimate births in bleeder circles is nearly *double* the ordinary average; and although some writers have been disposed to ascribe a teleological significance to this peculiarity by regarding it as a "remedium naturae" against the excessive mortality of bleeders, it is none the less clear that the interests of society are endangered by a provision—if it be such—which threatens to seriously increase the frequency of this fatal affection.

The first statistics on this point were published by Wachsmuth, and embraced only twelve marriages in bleeder families. From these marriages were born 114 children, or 9.5 children to each marriage; whereas the normal average of children born in wedlock is only about five. A later compilation by Grandidier showed 204 children to 21 bleeder marriages, or a ratio of 9.7 to 1; and a still later estimate 324 children to 36 marriages, or exactly 9 children to each marriage. These figures show, at all events, that the asserted fecundity of bleeder families is in all probability not imaginary, but real, and in some way intimately connected with the nature of the anomaly itself. What makes this peculiarity the more remarkable is the fact that most of the individuals who manifest it are not themselves bleeders, and yet are able to transmit the disease, the *latent* anomaly in their own persons appearing fully developed in their children.

The terrible importance of hæmophilia to the welfare of the

families concerned, on account of its markedly hereditary and dangerous character, would naturally lead us to expect that in many of these families full accounts of the existence of the affection in former generations would have been handed down through oral or even written tradition. In fact, several of these families possess records so complete in this particular that it has been possible to construct an actual *family tree of the disease*, with roots or main branches running back through several decades or even a century and upwards, and ramifying more or less widely in later times.

Thus, in the American bleeder families Smith-Shepard and Appleton-Brown, the disease could be directly traced through the entire interval from 1720 to 1806 (Otto, Hay); while of the two unrelated bleeder families at Tenna in Graubünden, one at least has been affected since 1770 (Vieli, Grandidier), and in the two families together the affection had gained such headway by the year 1854, that at Tenna alone, out of a total population of 165, there were at that date no less than fifteen bleeders. So also Dr. Schrey, who was himself a bleeder, informs us (Dissert. de hæmophilia. 1857. Berolini) that the disease could be traced in the widespread bleeder family to which he belonged in Mühlfurt (Rhenish Prussia) as far back as 1750. Other instances of a similar kind may be found in the statistical compilations of Grandidier (ll. cc.), which show that up to 1872 there were in all 73 carefully described cases possessing a clear genealogical record of the disease. That the results of investigation upon this point should have been less satisfactory in other cases, which were possibly just as truly of an hereditary character, is certainly not surprising, if we consider how few families are able to recall the pathological fate of their ancestors even when it has been of a peculiar character, and how very readily the *rudimentary* cases, which occur in bleeder families alongside of the marked forms of the disease, might be overlooked entirely. Still another difficulty arises from the fact that the disease is transmitted *indirectly* much more frequently than directly, since children naturally remember with less distinctness the diseases of their collateral relations than those of their parents. Finally, it is not to be forgotten that, as a rule, *the pedigree of the disease is not identical with the pedigree of the family name*, and that consequently the disease is more difficult to trace genealogically than it would be if it were transmitted only *agnatically*, *i. e.*, only through the male relatives bearing the family name. Experience shows, however, on the contrary (see further on), that the *cognatic* or maternal influence plays a far more important rôle than the agnatic in the propagation of bleeders; hence, we commonly find that, in consequence of the marriage of the females into other agnatic circles, the group of individuals which forms the *bleeder family*, and which is composed for the most part cognatically, is distributed among several families bearing different names. Numerous instances of this kind are to be found in the literature

of hæmophilia (see Grandidier); still the number of these, as well as of reported hereditary cases in general, would undoubtedly have been much larger if family traditions were not so commonly monopolized by the agnatic family history to the almost total neglect of the cognatic record.

2. *Sex.* The predisposing influence of the *sexual character* should be mentioned immediately after the family hereditary disposition, not only because it ranks next in importance, but also because it is ordinarily connected with the latter in a manner that is extremely characteristic. In general, it may be said at the outset that *fully developed hæmophilia occurs with very much greater frequency in male than in female individuals.* The evidence upon this point is overwhelming. The earliest cases, reported by Alsaharavi, A. Benedictus, Hoechstetter, and Banyer, were all *male* bleeders; while in recent times, Otto, Hay, Nasse, Wachsmuth, and many other writers, have specially insisted upon this peculiarity of the disease, and their opinion is amply confirmed by the large mass of evidence now in existence. Thus, a compilation of all the reported cases of *well-marked hæmophilia*, in which the sex was noted, discloses the remarkable fact that the *fully formed anomaly has been observed nearly thirteen times more frequently in male than in female individuals.*

Out of 650 of these cases there were only 48 females to 602 males—a proportion, therefore, of 1 to 12.6; or, expressed in percentages, 8 per cent. females to 92 per cent. males. In scarcely any other affection is the predisposing influence of sex so strikingly noticeable.

This prevalence of hæmophilia in the male sex is equally a characteristic of *individual bleeder families.* Thus, when several cases have occurred in a small circle of this kind, it is much more common for the *sons alone* to be affected, rather than the sons *and* daughters, or the daughters *alone.* When the disease appears in both sexes, moreover, the number of *male* bleeders usually far exceeds that of the female bleeders; and finally, the instances are much more numerous where *all the sons without exception* are bleeders than where the disease attacks *all the children* (both sons and daughters), or *all the daughters alone.* Such facts as these show clearly that the influence of sex in predisposing to the

anomaly in question is not merely a general law governing the gross statistics of the disease, but is likewise a radical differential principle, the operations of which are *special* in character, and discernible even in the smaller groups represented by the children of single families.

The statistical material available for the study of these special operations of the law is naturally much smaller than that which we were able to use above for the general comparison, since most of the reports of bleeder families fail to give the number and sex of the children who are not bleeders. Still, taking the instances compiled by Grandidier in which these particulars are noted, and adding the instances recently recorded, we have a total of 76 bleeder families available for our purpose. In these families the comparative distribution of the disease between sons and daughters was as follows:

Sons were affected in	70	families.
Daughters were affected in	15	"

In children of the same parents, therefore, the disease occurred 4.7 *times more frequently in the sons than in the daughters.*

Sons alone affected in	61	families.
Sons and daughters both affected in	9	"
Daughters alone affected in	6	"

Consequently the *sons alone* were affected 6.8 times more frequently than the sons and daughters together, and 10.2 times more frequently than the daughters alone.

Furthermore, the composition of the 76 families with respect to the sex of all the children (bleeders and non-bleeders) was as follows:

Sons and daughters both	60	families.
Sons alone	13	"
Daughters alone	3	"

Now, we have seen above that out of these sixty families containing children of both sexes, there were only nine instances in which both sexes were affected; this leaves fifty-one instances in which the disease was confined to the sons, notwithstanding the coexistence of daughters. Consequently, in families containing children of both sexes the affection occurred 5.7 times more frequently in the sons alone than in the sons and daughters together. Again, with respect to the limitation of the disease to the daughters, we find that out of the six instances mentioned above, three occurred in families which contained no sons, leaving only three instances, therefore, in which daughters were exclusively affected, notwithstanding the coexistence of sons. It is clear, therefore, that when children of both sexes existed, the exclusive limitation of the disease to the sons occurred far more frequently than the exclusive limitation to the daughters, for the former occurrence

was noticed fifty-one times out of a possible sixty, and the latter only thrice—a relative proportion of seventeen to one.

The prevalence of male bleeders among the children of the same parental pairs is shown also by the following table, giving the comparative numbers of male and female bleeders in the nine families in which *the sons and daughters were both affected:*

Total number of *male* bleeders in these nine instances............	40
" " *female* " " " "	11

The total number of bleeder sons, therefore, in these circles of brothers and sisters was 3.6 times larger than that of the bleeder daughters.

Furthermore, in the fifty-nine instances in which *sons only* were affected and the exact number of these bleeders was stated, we find:

Total number of bleeder sons.............................. 170

or nearly three bleeder sons to each marriage.

On the other hand, in the six instances in which *daughters only* were affected, and the exact number of these bleeders was stated, we find:

Total number of bleeder daughters........................... 9

an average of only 1.5 bleeder daughters to each marriage.

It appears, consequently, that the average number of female bleeders, when the disease is limited to the daughters in families containing children of both sexes, is only half that of the male bleeders in the much more frequent (nearly ten times more frequent) opposite cases in which the sons only are affected. It would seem, therefore, that the influence of the female sexual character in preventing the occurrence of fully developed hæmophilia makes itself felt even when in a particular family circle a special tendency to the production of female bleeders can be recognized, since the tendency in most of these instances is restricted to much narrower limits than is the case with the male bleeders.

Finally, the preponderance of male over female bleeders is also shown by the fact that the *implication of all the sons* in a given family is *much more frequent* than the implication of *all the children* (both sons and daughters), or of *all the daughters alone.* While the former event, according to reliable accounts, has happened twenty-seven times, the implication of all the children has occurred only three times, and that of all the daughters alone only four times. Three out of these last four families, it will be remembered, contained no sons, while of the twenty-seven families in which all the sons were bleeders, there were only eight in which no daughters existed.

Now, although the foregoing details prove beyond the least question that the female sex is far less subject than the male to *fully-developed* hæmophilia, it is still not to be overlooked, on the other hand, that the actual share of the female sex in the

entire number of cases, which probably belong to the *pathological domain of hæmophilia*, is in all probability considerably larger than appears from the statistics already given, or than can possibly be shown statistically. For all the cases thus far considered represent only the completely developed form of the disease, that is, only such varieties of hemorrhagic diathesis as are demonstrated to be genuine hæmophilia by their congenital and habitual character. In addition to these, however, there is a large number of *rudimentarily developed* and *anomalous* cases, whose identity with hæmophilia is far less clear, and *whose comparative frequency therefore in the two sexes we have no means of determining with accuracy.* Still, as Grandidier has pointed out, it is possible that such rudimentary cases, particularly those in which a certain degree of bleeder disposition is manifested only transitorily and at certain times (*e. g.*, at the first appearance of the menses, in childbirth, etc.), are really more frequent in females than is commonly supposed, the true relation of these attacks to hæmophilia being overlooked in consequence of their trifling nature or brief duration. Of course, we are far from advocating the indiscriminate admission of every transitory hemorrhagic diathesis of this kind to the category of hæmophilia ; on the contrary, the position assumed earlier in this article is ever to be kept in mind, viz., that the *congenital* and *habitual* character enters into the definition of the bleeder disease as an essential element, and that probably in all cases hæmophilia is to be regarded as an affection which depends upon an *original and permanent structural vice.* Only those cases of transitory hemorrhagic diathesis, therefore, can be properly admitted which are fairly entitled, *notwithstanding their temporary clinical character*, to be considered as merely the momentary expression (or, more correctly, "the outbreak") of a really permanent, though usually *latent*, morbid disposition. We are clearly warranted, however, in suspecting the existence of a *congenital* disposition to hemorrhages, and therefore hæmophilia, whenever the individual, male or female, who is *momentarily* the subject of a severe and almost uncontrollable hemorrhage, without ever having suffered from decided hæmophilia (*habitual* hemorrhagic diathesis), *comes from a bleeder family*,

perhaps has bleeder brothers and sisters or bleeder children; in short, therefore, whenever such a patient, notwithstanding his apparently perfect health in other respects, still *stands under the ban of an hereditary tendency to attacks of dangerous bleeding.*

These *etiological considerations*, as we have already intimated at the outset of the present chapter, certainly point to the desirability of enlarging our conception of hæmophilia in some way so as to include at least all those imperfectly developed cases of hemorrhagic diathesis which exist alongside of the complete forms of the disease in both sexes among the members of bleeder families, and manifest themselves at some time or other by actual clinical symptoms (hemorrhages). Still, any attempt to introduce these rudimentary cases into the statistical register of hæmophilia would be thwarted, not only by the want of exactness in existing observations, but also more especially by the fact that these cases in their minor degrees of development, such as are seen with special frequency in females, are entirely indistinguishable from a condition of *apparent good health*, or, in other words, from a *complete latency of the congenital bleeder disposition.* So long, however, as we are unable to compute these rudimentary cases, an *exact* calculation of the comparative frequency of hæmophilia in the two sexes is obviously out of the question, and would doubtless remain so even if we possessed—as we certainly do not—a record of all the fully developed forms of the disease. Still, there can be no reasonable doubt of the very marked preponderance of frequency of the disease in the male sex.

The expressions used above—*apparent good health*, or, still better, *complete latency of the bleeder disposition*—were employed in contrast with the attribute of *actual* and *perfect* health, for the purpose of designating the bodily condition common to *all those members of bleeder families, who, without being themselves bleeders, are still able to transmit the anomaly hereditarily to their own offspring.* We have already seen that the propagation of hæmophilia takes place in reality far more frequently by indirect than by direct transmission, that is, rather through the non-bleeder brothers and sisters than through the

bleeders themselves. Now, to abandon the law of continuity in these cases, and to suppose that the disease constantly passes over the intermediate members and renews itself de novo, is certainly contrary to our fundamental conceptions of natural processes. In fact, the undiminished severity with which the disease reappears in the children of these individuals, compels us to infer that the soundness of the latter is not actual, but only "apparent," and that they are really subjects of a *latent* bleeder diathesis. It is clear, however, that if we are to take into consideration the *nature*, and not merely the external manifestations of the anomaly, we shall strictly be compelled to include in the category of hæmophilia also all those *completely latent* cases in which individuals who have never themselves bled in a morbid manner continue to give birth to one child after another bearing the unmistakable impress of the disease. Regarded in this light, the relative shares taken by the two sexes in the affection appears widely different from those shown by statistics which deal solely with the external phenomena of hæmophilia, and the highly interesting fact is disclosed that *the female sex is in reality to be regarded as the more intensely affected, because it possesses in a far higher degree than the male*, not merely the opportunity, *but also especially the capacity for transmitting the disease by inheritance to its own offspring.* For, in by far the majority of instances where hæmophilia is transmitted to one or more children, and where consequently a *multiplication* of individual cases of the disease takes place, this result is brought about, not through a male (bleeder or non-bleeder) member of a bleeder family, but directly through a *female* member. That this peculiarity, moreover, is by no means wholly dependent upon the excessive premature mortality of the (mostly bleeder) male members of these families, but is rather directly connected with a more active *transmitting power* on the part of the female members, is apparent from the following important and interesting facts (Grandidier):

1. *Males* in bleeder families, *who are themselves bleeders, do not*, as a rule, beget bleeder children by women who belong to non-bleeder families; in fact, *the children in this case are usually healthy and non-bleeders.* On the other hand, *the children*

of women who are themselves bleeders are quite uniformly subjects of hæmophilia.

2. *Males* in bleeder families, *who are not bleeders, almost never beget bleeder children* by women from other families. On the other hand, among the *children* of *women* who belong to bleeder families, *without being themselves bleeders, there are almost always some who suffer from pronounced hæmophilia* (see above).

It is clear, therefore, that in the transmission of hæmophilia the *maternal* influence is far more important than the paternal, for while the female members of these families appear to be capable of propagating the disease, whether they are bleeders or not, the males rarely manifest this capacity except when they are themselves bleeders, and even then the chances of transmission are much less than in the case of a latent disposition on the mother's side. Since now, as we have already remarked, the females are rarely fully developed bleeders, and the male bleeders either die prematurely, or, as a rule, fail to reproduce the disease in their children, it follows that *the non-bleeder women in bleeder families are in fact the most frequent* and *most efficient* "*conductors*" (Vieli, Grandidier) of hæmophilia, and that to them the hitherto constantly increasing spread of the affection is mainly due.

In the two large bleeder families at Tenna, in Graubünden, Vieli found that the *males had never transmitted* the disease, although they had *all been bleeders* with but a *single* (!) exception, their children by intermarriage with other families having been *invariably sound* and free from hæmophilia. On the other hand, during the entire period of the existence of the disease in these families—nearly a century—*none* of the *women*, so far as could be discovered, had ever clearly manifested the bleeder diathesis; and yet, with the single exception referred to, the sons of these non-bleeder women had all been bleeders. In other families, however, an *agnatic* transmission of the disease, that is, from father to son, has been observed in several instances (Schuenemann, Reinert [ll. cc.], etc.); still, such an occurrence is comparatively rare, while the appearance of hæmophilia in the children of non-bleeder males in hæmophilist families is so very exceptional that Grandidier expressly mentions[1] his inability to find a single example among the numerous cases of hæmophilia reported in Germany and Switzerland. Isolated instances of the kind have, however, been observed by English writers, particularly Legg.[2] There seems to be no reasonable doubt, therefore, that *the most frequent mode of propagation of hæmophi-*

[1] Schmidt's Jahrbücher. CLIV. S. 96.

[2] l. c. p. 127.

lia is by means of indirect transmission in a cognatic direction ; hence the appropriateness of the term "conductors," which was first employed by the inhabitants of Tenna, and afterwards became generally adopted as a designation for the non-bleeder women of hæmophilist families through whom the disease is transmitted.

3. *Age.*—Inasmuch as hæmophilia is probably always of congenital origin, we can properly speak of a predisposing influence of age only in so far as the *first outbreak* of the affection tends to occur at *particular* epochs in the physiological course of the vital processes *more frequently* than at others. Now, all observations go to show, as we have already intimated (see Definition of the Disease), that the first bleedings of hæmophilia, in by far the majority of instances, take place in *very early childhood*, and are decidedly rarely postponed to a later period. Still, except from traumatic causes, marked hemorrhages of this character do not often make their appearance so early as immediately during birth, or during the first few days or weeks of life, while the occurrence of the so-called spontaneous bleedings at these times is quite exceptional. At all events, as Grandidier particularly insists, the great majority of the so-called spontaneous *umbilical hemorrhages* of new-born children are not to be considered, notwithstanding their apparently congenital character, as the manifestation of an actual bleeder diathesis, since they are not specially frequent, but rather rare in bleeder families, and are, moreover, not apt to be followed in after-life by an habitual disposition to hemorrhages. On the other hand, as was indirectly intimated above, traumatic hemorrhages of an obstinate and even fatal character have been repeatedly observed in the children of bleeder families after the most trifling wounds. Thus, quite a number of deaths have been reported in Jewish families from the rite of circumcision on the eighth day, as well as similar results in other families from cutting the frenum linguæ soon after birth, or from accidental wounds (see the fuller consideration of this point under the Terminations of the Disease). While it is evident, therefore, that the congenital bleeder diathesis may manifest itself under favoring circumstances very prematurely, the most common time for the full outbreak of the disease is at the end of the nursing period, or *at the beginning of the first dentition*, not only because the traumatic bleedings now become more frequent in

consequence of slight contusions, excoriations, etc., but especially also because about this time the apparently spontaneous bleedings begin to make their appearance. Occasionally these latter hemorrhages do not occur until the second year or even later, while in its subsequent course the disease, notwithstanding its essentially stationary character, frequently presents fluctuations, with periods of aggravation, during which the bleedings are more frequent and more readily produced, present a more obstinate character, and are specially dangerous to life. Accordingly we find that there are certain ages, viz., those with which these periods of aggravation usually coincide, when the disposition to bleedings is particularly marked. Thus, Grandidier calls attention to the fact that *the second dentition*, *puberty*, and in females *the first appearance and the cessation of the menses*, are specially critical periods for these patients; and although this rule is not without occasional exceptions, its general correctness is proved by the experience of most of the reported cases. Finally, it is also to be noted that *with the advance of age there is very generally a gradual decline in the average intensity of the affection*, and that accordingly the *manifestations* of the congenital anomaly are commonly found to be most marked in youth, and to become much feebler as the individual approaches middle life. In exceptional instances, however, the symptoms of hæmophilia recur again and again with undiminished intensity up to old age, and even at this period death may result directly from one of the hemorrhages.

As regards the *relation which the spontaneous umbilical hemorrhages of new-born children bear to hæmophilia*, it appears from the investigations of Grandidier[1] in 228 cases of hemorrhagia umbilicalis neonatorum, that out of this number only 14 occurred in bleeders belonging to eleven different bleeder families, and that nearly 94 per cent., therefore, of these hemorrhages were due not to hæmophilia, but to other causes. Moreover, on comparing this statistical result (14 cases of umbilical hemorrhage in eleven bleeder families) with the large number of cases of hæmophilia thus far carefully reported (650 cases in 219 families), it is evident that this form of hemorrhage is far from common in bleeder circles, and is very much less frequent than the traumatic and spontaneous hemorrhages.

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[1] Die freiwilligen Nachblutungen der Neugeborenen. Cassel, 1871; also Schmidt's Jahrbücher. Bd. CLIV. p. 95.

With respect to the time of the first outbreak of the affection, exact data are wanting in a large proportion of the reported cases. Still, in most of the accounts it is stated that the individuals affected had been subject to dangerous hemorrhages "from early childhood." In 95 cases, however, Grandidier succeeded in ascertaining the time when the first hemorrhage occurred, as shown in the following table:

In the 1st year of life........	58 times.	In the 9th year of life........	1 time.
" 2d "	8 "	" 10th "	4 times.
" 3d "	3 "	" 11th "	1 time.
" 4th "	2 "	" 12th "	1 "
" 5th "	5 "	" 14th "	1 "
" 6th "	5 "	" 15th "	1 "
" 7th "	1 "	" 17th "	1 "
" 8th "	1 "	" 22d "	2 times.

According to this table 69.5 per cent. of the first outbreaks occurred in the first two years of life, and 61 per cent. in the first year alone. In all probability, however, the share of the first year would be much larger if the statistical material were sufficiently extensive to give the true percentages. Furthermore, it is to be particularly noted that the twenty-second year appears to be the very latest limit up to which the congenital and hereditary disposition to hæmophilia can remain latent, and thereafter develop into the pronounced and habitual disease. For, even in the cases in which the date of the onset of the affection has not been recorded, it is reasonably certain from statements in the reports that the anomaly had already manifested itself in childhood and youth, and, therefore, previous to the twentieth year. Whether, however, the same rule holds good also for those rudimentary forms of the disease whose manifestations are often of only a transitory nature, and whose only claim to be regarded as hæmophilia rests upon the fact that the affected individuals belong to bleeder families, must for the present remain undetermined.

4. *Constitution*, *Habitus*, *Temperament.*—There appears to be no one definite form of *physiological constitution* which exhibits a specially marked predisposition to hæmophilia; on the contrary, the varying accounts given by writers of the condition of the bodily functions in bleeders and bleeder families render it probable that, apart from the tendency to dangerous hemorrhages which characterizes the pronounced form of hæmophilia, and the capacity for transmitting the anomaly inhering even in individuals with the latent disposition, the constitution of bleeders may differ widely in individual cases. Some authors, it is true, have

distinguished, according to the nature of the constitution, two distinct forms of hæmophilia, viz., an *erethistic* and a *torpid* variety, and have maintained the greater frequency of the latter, that is, the more frequent coincidence of hæmophilia with torpor of the vital processes. We fail, however, to find any warrant for such a distinction; indeed, the very fact that the affection occurs as well in connection with a more active flow of the vital processes—the so-called erethismus of the constitution—shows conclusively that no essential etiological relation exists between hæmophilia and either of these constitutional states; not to mention that the terms themselves, "erethismus" and "torpor," have been and still are frequently used without any clear conception of their meaning.

Just as it is highly probable, therefore, that there is no special form of constitution[1] by which bleeders are characterized, so these individuals possess no distinguishing *habitus*. The muscular and osseous systems may be strongly or imperfectly developed, and while a tendency to obesity is noticeable in many cases, in others it is wanting. Some writers have attached importance to the *color* of the *hair*, *skin*, and *iris*, and assert that *blond* or *reddish* hair, a *pale* and *but slightly pigmented* skin, and *blue* eyes, are particularly frequent in bleeder-families; still the disease is by no means uncommon in dark-haired, brunette individuals with brown or black eyes. One peculiarity, however, viz., *a certain delicacy and transparency of the general integuments, together with a superficial position and marked fulness of the subcutaneous vessels, particularly the veins*, is mentioned by trustworthy observers (Otto, Nasse, Wachsmuth, Schönlein, Virchow, Grandidier, Vieli) as so commonly noticeable in bleeders, that we can scarcely deny it a certain causal relation to the bleedings of hæmophilia, especially since these peculiarities in the position and fulness of the superficial vessels are accompanied also by *certain anomalies in the structure of the coats of the vessels* (see Anatomical Changes), which may likewise be urged with some force in favor of a *vas-*

[1] The word constitution is used here as in Vol. XVI. (p. 252), to express the sum-total of the vital processes in relation to the mass of matter set in motion, and the velocity and direction of its movement.

cular theory of hæmophilia, and at all events deserve full consideration.

Finally, as regards the *temperament* and *mental endowments* of bleeders, no universal or even general rule can be deduced. Whether, as asserted by some writers, a *phlegmatic* temperament is really "somewhat" more common in these patients than the choleric and sanguine, must for the present remain doubtful; certain it is, however, that in several instances the individuals are described as very vivacious, and possessing an ardent, even passionate disposition (Wachsmuth). Inasmuch, therefore, as the most diverse forms of temperament are compatible with the bleeder disposition, it is hardly likely that we shall discover any important predisposing factor in this direction. Nor is the inquiry more promising when we come to the mental endowments, for although some bleeders are described as deficient in intelligence, others are highly spoken of for their clear-headedness, quick perception, artistic talents (music, painting, "versification"), etc.; indeed, it must be evident from the contrariety of these descriptions, interesting as such *hors-d'œuvres* undoubtedly are in the histories of patients, that little or nothing is added by them to our knowledge of the etiology of hæmophilia.

5. *Race and Nationality.*—The scantiness of accurate reports as to the occurrence and frequency of hæmophilia in numerous non-European countries—as was noticed in our introductory sketch of the geographic distribution of the disease—makes it impossible to decide whether *race* really exerts a predisposing influence or not. Still our sketch, it will be remembered, revealed at least one interesting fact, viz., that in those portions of the Old and New World which are inhabited by Europeans or persons of European descent, the frequency of the disease appears to be largely influenced by the *nationality* of the population, the *Anglo-Germanic* race exhibiting a special disposition to the affection. A similar predisposition, it may be added, seems to exist also in the widespread *Jewish* race, since as we have already seen, the disease has been repeatedly noticed among this people in connection with the rite of circumcision, while of the total number of bleeder families thus far reported a consider-

able proportion have been Israelites (Grandidier). With these remarks we must dismiss the subject of predisposing influences, and pass now to a brief consideration of the *determining causes* of hæmophilia.

B. *Determining Causes.*

Under this head are to be included all influences which appear either to develop *hæmophilia de novo*, *i. e.*, to induce its *first* appearance in a family circle, or to awaken the *latent* disposition to an actual outbreak.

With respect to the *primordial* causes of hæmophilia, we are still in complete ignorance; nor does the origin of the disease in any considerable number of families appear to have been due to their common exposure to influences of a similar character. It is clear that in an affection which, like hæmophilia, apparently always depends upon a congenital morbid idiosyncrasy, the *physical peculiarities of the parents* (in cases where the disease occurs to all appearance spontaneously in the children *without evident hereditary transmission*) certainly deserve special attention. Investigation upon this point has, however, failed to give any uniform result, the parents and ancestors in some of these cases having according to all accounts enjoyed perfect health, while in others various family diseases are mentioned, as gout, scrofula, and affections of the heart and lungs (Grandidier). Furthermore, the opinion entertained by some writers (Harris)[1] that *consanguineous marriages*, to which so many other disastrous results are ascribed, induce also hæmophilia in the offspring, has by no means been proved, although coincidences of this kind may be occasionally noticed; nor is there anything in the records of individual cases, or of series of cases, to show that any other fact whatever, external or internal, concerned in *procreation* and *conception*, could have played a definite rôle in the etiology of the disease. Finally, *influences upon the mind of the mother during pregnancy*, especially such

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[1] Philadelphia Medical Times. Vol. II. p. 38.

as excite *violent emotions* (terror, anger), have also been regarded as determining causes of hæmophilia by many writers (Mützenbecher,[1] André[2]); still, the facts in such cases are so apt to be distorted by the influence of preconceived opinions that it is easy to imagine a genetic relation where there is really nothing but the operation of mere chance.[3]

It must probably be admitted, therefore, that the entire question as to the nature of the influences which operate *originally* in the genesis of hæmophilia still remains to be settled, and that the pathology of the disease, so far as regards this vital point in the etiology, is still wrapt in complete obscurity. On the other hand, the *determining causes of the bleedings*, that is to say, the influences which are able to excite an outbreak, when the disposition, however acquired, already exists, are much better understood, and are briefly as follows:

The characteristic hemorrhages of hæmophilia are most generally induced by *injuries* which sometimes produce an actual solution of continuity with *escape of blood upon the surface*, at other times merely an *interstitial extravasation* without any true wound (solution of continuity). Cuts, punctures, incised or lacerated wounds, contusion and wrenching of the external soft parts by pressure, blow, or more forcible lateral displacement, may all act as exciting causes; while as regards the mode in which these causes operate in bleeders it is especially characteristic that extremely obstinate and copious external hemorrhage, as well as a very extensive interstitial hemorrhage, occurs in these individuals not only after severe wounds and injuries, but quite commonly also even after the most *insignificant traumatic accidents*. Indeed, it seems as if it were just these very trifling

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[1] Dissertatio de Hæmorrhagicis. Heidelberg, 1841.

[2] *Schmidt's* Jahrbücher. Bd. LXXII. S. 192.

[3] *J. Wickham Legg*, in his admirable Treatise on Hæmophilia, London, 1872, p. 35, after taking essentially the same ground as the above, adds: "It is well, nevertheless, not to lose sight altogether of the influence of the emotions, especially of the depressing emotions, in the production of hemorrhage. A sudden great fear is not uncommonly the starting-point of a hemorrhagic disposition in women; and the emotions of grief and anger may be followed by hemorrhages. I believe that the emotions have a far greater influence upon the tissues than is generally thought."—TRANSLATOR'S NOTE.

injuries, so harmless in healthy persons as to scarcely attract attention, that are specially dangerous in bleeders; in fact, the mortality statistics of hæmophilia show that fatal hemorrhage results far more commonly from very slight than from severe wounds. Still we are not to conclude that the latter are unattended by danger to bleeders; on the contrary, such wounds have been found to result fatally more frequently in them than in other persons (Grandidier), although the difference between bleeders and non-bleeders in respect to the clinical course of these more serious wounds and injuries naturally attracts less notice, for the reason that the latter are also dangerous even for non-bleeders. Add to this the further fact that with prudence on the part of the patient important lesions are far less likely to be met with than those of a very trifling character, and we have some explanation why it is that certain writers (Fordyce, Coates, Allan, Wachsmuth) have laid so much stress on the danger of insignificant, and so little upon that of serious injuries.

There is certainly no doubt, however, that the most trifling lesions in bleeders may be followed by extremely alarming results, and in this respect the descriptions which these writers have given are by no means exaggerated. Thus, simple punctures, the opening of small superficial abscesses, the application of leeches and cups, the extraction of teeth, the cutting of the frenum linguæ in young children, the ritual operation of circumcision in Jewish bleeder children, as well as numerous other very trifling *operative* procedures, have been followed by uncontrollable and ultimately fatal hemorrhages in so large a number of cases, that any operation upon these patients, however slight, attended by bleeding, must be regarded as dangerous. The same is true also in regard to slight *accidental* wounds of all kinds (pin-pricks, superficial abrasions of the skin, trifling contusions, etc.); these are likewise very apt to be followed by most obstinate and alarming external hemorrhages, or by very diffuse ecchymoses of the soft parts; in fact, the much greater difficulty or even impossibility of avoiding such accidents makes them a specially frequent source of danger. Certain of these minor wounds (both the operative and the accidental) seem to be attended, as a rule, by much less risk than others. For example,

circumcision, the extraction of teeth, and accidental wounds of the head and face are spoken of as exceptionally dangerous in bleeders, while venesection and vaccination are regarded as less hazardous. Still, there are distinctions based entirely upon the hitherto observed rates of mortality, and consequently upon the *prognostic* differences which naturally exist between the individual forms of hemorrhages according to their *nature* and *location*, and do not materially alter the fact that even the forms which are alleged to be harmless, *e. g.*, those following vaccination, may at times be characterized by *unusual abundance and obstinacy* (Dequevauviller, Tardieu, Thal, Vieli), and, like the others, may even run a fatal course (Alsaharavi, Otto, Hughes, Miling, Rieken). Indeed, all clinical observation shows that any *traumatic lesion* in a bleeder, whatever its cause or situation, may excite a *characteristic* hemorrhage (external or interstitial), and may, therefore, be regarded as a *possible cause of a hæmophilia bleeding.*

A remarkable exception to the general behavior of traumatic hemorrhages in bleeders seems to be presented, to a certain degree, by that attending the operation of *vaccination.* At least the reported cases of profuse bleeding after this operation have been exceedingly rare, two only having been recorded in the entire literature of hæmophilia (Heyfelder,[1] Stromeyer[2]). It is a curious fact in this connection that Rieken was so well satisfied of the innocuousness of vaccination in bleeders that he even recommended the operation as a prophylactic against further hemorrhages.[3]

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[1] Med. Vereinszeitung. 1833. No. 48.

[2] Die chirurgischen Krankheiten des Kopfes. 1864. S. 120.

[3] Another instance of the danger occasionally attending vaccination in bleeders deserves to be mentioned here. In a case of marked hæmophilia attended by Dr. W. G. Wylie, and seen also by Drs. Van Buren, Keyes, and myself (all of New York), it was ascertained that the patient, a young lady, had nearly bled to death from vaccination when six weeks old, and that several subsequent attempts at vaccination had all been attended by alarming hemorrhages; none of the attempts were successful. In later life repeated and profuse hemorrhages had occurred from the nose, gums (after extraction of a tooth), and bowels. During the summer of 1877 the patient died from peritonitis, suspected to have been excited by hemorrhage into the peritoneal cavity(?). This case, which Dr. Wylie informs me he intends to report in full, is unusually interesting, not only from the sex of the patient, and from the fact that the mother was also a marked bleeder, but also because this instance of the disease breaks the long silence of American reports of hæmophilia.—Translator's Note.

As regards the *modus operandi* of traumatic influences, it is noticeable also, according to trustworthy observers (Wachsmuth, Martin, Grandidier), that *the danger from the same kind of wound*, as a leech-bite or the prick of a pin, *is not equally great at all times*, and that *the disposition to bleeder hemorrhages after wounds seems to vary considerably at different times.* In our consideration of the predisposing causes particular attention was called to the existence of certain *periods of life* (p. 25) which are excessively dangerous and critical for bleeders, because traumatic hemorrhages occurring at these times present a specially marked bleeder character; it may be added here that variations in the individual disposition to serious hemorrhages after wounds are likewise occasioned by other causes, the nature of which we are still unable to determine with certainty. Krimer's conjecture that the *change of the moon* exerts an influence upon the intensity of the hemorrhagic disposition seems to us scarcely compatible with present scientific conceptions. More credible, perhaps, are the statements of other writers, that traumatic hemorrhages in bleeders are more severe during *changes of the seasons*, in spring and autumn (Consbruch, Rieken, Wachsmuth, Grandidier, Martin), or *during the sultriness of air preceding a thunderstorm* (Martin); still, the evidence of a determining influence on the part of these *atmospheric* conditions is too imperfect to warrant us in accepting it as conclusive.

There remains to be considered another point of importance in this connection, viz., the influence of traumatic hemorrhages in *modifying the future character of the disease.* Almost all writers testify that the *occurrence of a traumatic hemorrhage* not only at times awakens a hitherto latent hæmophilia, but also *materially aggravates, at least for the time being, the manifestations of an already developed hemorrhagic diathesis.* Thus, it has been noticed by Virchow, Grandidier, and others, that after the occurrence of a traumatic hemorrhage the patient is specially subject to the so-called *spontaneous hemorrhages*, both those in which the blood escapes externally and those of an interstitial character. Still the precedent occurrence of a traumatic hemorrhage is not essential to the development of these spontaneous bleedings; they may occur independently of such

a connection, and may even constitute the initial manifestation of the disease.

While, therefore, for many of these spontaneous hemorrhages we are able to find a determining cause in the previous occurrence of a traumatic bleeding, in other instances unpreceded by an event of this kind, we are naturally compelled to search for other explanations. In these cases it is to be noted particularly that sometimes the hemorrhage occurs without any demonstrable exciting cause, and especially without prodromata, suddenly, as it were *of its own accord;* at other times, and in fact *more frequently*, the patient complains, before the hemorrhage, of *flushings*, a *sensation of heat*, and *more forcible pulsations of the heart and arteries;* the face, especially the cheeks and the lobes of the ears, is markedly reddened and feels hot; there is also headache, together with sensitiveness of sight and hearing and mental excitement—symptoms, however, which usually all gradually decline and entirely disappear when the bleeding is once established (Buel, Elsässer, Rieken, Davis, Wachsmuth, Uhde, Virchow, Grandidier, and others). Now these molimina, which evidently stand in an indirect causal relation to the ensuing hemorrhage, are obviously to be interpreted as the expression of an increased arterial tension, perhaps also of an abnormal fulness of the entire vascular system; hence the spontaneous hemorrhages which are thus characterized may properly be distinguished as *fluxionary* (Virchow) or possibly even as *plethoric* hemorrhages. The pertinency of these designations is shown, moreover, by the fact observed by Grandidier that many of these hemorrhages are very clearly induced by influences which excite a more forcible action of the heart (the use of alcoholic stimulants, mental emotion, physical exercise), or which suddenly increase the mass of the blood (copious drinking). It is noticeable, on the other hand, that these prodromata—the molimina above described—are rarely observed when the spontaneous hemorrhages have been preceded by a trauma, for the reason that, under these circumstances, the anæmic condition of the patient naturally precludes any considerable congestion, particularly any plethora.

To summarize, finally, our present knowledge of the exciting

causes of the hemorrhages of bleeders, the result is briefly as follows:

> In bleeders the hemorrhages are most frequently of a directly *traumatic* origin, but they may also occur without the reception of any wound or mechanical injury (spontaneous hemorrhages). Still, many of even the latter hemorrhages are *indirectly* traceable to the influence of a recent wound, since it is found that after such an event the tendency to spontaneous hemorrhages is considerably increased, or, it may be, is for the first time awakened. When, on the other hand, there has been no antecedent traumatic hemorrhage, the spontaneous bleedings generally manifest a distinctly *fluxionary* character, and are preceded by various symptoms of congestion and plethora. Finally, in rare instances the spontaneous hemorrhages seem to occur *independently of any manifest external or internal cause*, with every appearance therefore of actual spontaneity, and must accordingly be regarded, until the subject is better understood, as the result of *unknown* influences.

Pathology.

Description of the Disease and Symptoms.

Since hæmophilia, as was insisted upon at the very outset of our subject, is not, properly speaking, a morbid process in the ordinary sense, *i. e.*, a constantly changing pathological event with a typical course, but rather an abnormal state of the corporeal organization or a *morbid disposition*, it is evident that the manifestations of this somatic vice may be modified in an unusually varied manner, according to the other external and vital conditions of the individuals affected. A complete *picture of the disease* is therefore out of the question, and we shall accordingly confine ourselves, first, to a statement of the *nature and general type* of the pathological symptoms by which the anomaly usually manifests itself, with a somewhat full description of

their *most important* characteristics; and secondly, but with less detail, we shall consider the special modifications which the typical manifestations of the anomaly are found to undergo according to the time of their occurrence, their determining causes, their particular localizations, etc.—in brief, therefore, according to their *accidental* relations.

The symptoms of hæmophilia, as the usual name of the affection denotes, and as we have repeatedly had occasion to mention, are essentially of a *hemorrhagic* character, so that the following sketch of the symptomatology will consist in the main of a more complete description of the hæmophilia bleedings, which, according to their anatomico-clinical aspects, may be divided into two leading varieties: first, the *external* hemorrhages, in which there is an extravasation of blood upon the free surface of the bleeding part; and secondly, the *interstitial* hemorrhages, in which the blood penetrates into the interstices of the bleeding tissue. While this generally adopted distinction will be observed in the following remarks, it should be borne in mind at the same time that the same bleeding-point not infrequently gives rise to both varieties of hemorrhage; for example, an external bleeding may be followed by a hemorrhagic infiltration of the bleeding tissue, and, on the other hand, after an interstitial hemorrhage the blood may ultimately force its way to, and stream from, the bleeding surface.

Most of the hemorrhages can, however, be referred without much difficulty to one or the other of these categories, or at least belong in *their main features* to one rather than to the other, so that we are on the whole practically justified in considering the two forms separately. A still more urgent reason for this course is the difficulty of adequately describing, by any other method, the important clinical differences which the two forms of hemorrhage present, not only with respect to their usual situation, but also in their entire mode of progress and their concomitant symptoms.

1. *External hemorrhages.*—These may be subdivided, according to their genesis, into the *traumatic* and the so-called *spontaneous* hemorrhages (see Etiology). In the *first* variety, the *location* of the hemorrhage depends upon the site of the lesion,

and is therefore unrestricted, since wounds may naturally occur in any part of the body. It is obvious, however, that traumatic external hemorrhages must take place most frequently from the *skin* and *superficial parts*, because these by their very position are most exposed to injuries likely to excite hemorrhage.

Finally, in this form of hemorrhage, the bleedings are much more frequently *single* than multiple, as might naturally be expected from the fact that they are usually due to very trifling accidents, and are confined to the immediate site of the lesion; so that we never meet with several bleedings of this kind occurring at the same time, except in those rare instances in which wounds have been inflicted *simultaneously* on different parts of the body. The behavior of the *spontaneous* superficial hemorrhages, on the other hand, is somewhat different in these respects. Thus, there is not only a more definite and more pronounced predilection for certain parts of the body and for certain tissues, but also a more frequent tendency to the occurrence of simultaneous hemorrhages from different localities. The favorite situation of these hemorrhages is the *mucous membranes*, particularly those of the *nasal* and *oral* cavities (the gums); next in frequency, those of the *genito-urinary apparatus*, *bronchi*, *stomach*, and *intestines;* more rarely the *conjunctivæ* and the *skin of the external auditory passage*, and still more rarely the *external skin*, provided its normal histological structure and its natural resistance and vascularization have been preserved. On the other hand, these hemorrhages are comparatively frequent wherever the skin has been inflamed, ulcerated, or filled with blood from an interstitial hemorrhage, or where there are recent, still highly vascular cicatrices resulting from previous wounds. In certain bleeders, however, bleedings which are independent of any wound, and which may therefore be regarded as spontaneous, take place from the intact skin of the tips of the fingers, the toes, lobes of the ears, nose, and back of the head (Coxe, Merkel, Adelmann). Rarest of all appear to be the extravasations of blood into the *internal* cavities; at least only a few cases of this kind have been described in the entire literature of hæmophilia. The comparative infrequency of these hemorrhages is naturally to be explained by the more protected posi-

tion of the cavities concerned; still, the very fact that hemorrhages do occur also in these more deeply-seated localities, shows that the bleeder diathesis is not confined to the superficial parts, but is quite general, and extends to all regions of the body.

Of hemorrhage into the *abdominal cavity* two cases have thus far been directly observed (Grandidier, Lemp, ll. cc.), in one of which blood was extravasated at the same time into the tunica vaginalis testis. A third instance of peritoneal hemorrhage was not directly observed by the writer who reported it (Brigstock, l. c.), but its occurrence was inferred from the history of the case.—Of *intermeningeal* apoplexies in bleeders only four cases are recorded (Wilson (2), Cousins (1), Tranéus (1);[1] while of hemorrhages into the *pleural and pericardial cavities* not a single one is reported. On the other hand, judging by the clinical symptoms in the large number of cases in which bleeders have suffered from inflammatory arthritic affections (see Complications and Sequelæ), it is highly probable that sanguinolent effusions into the various synovial sacs have been of frequent occurrence (Dubois,[2] Ammann,[3] Assmann[4]), although as yet this point has not been demonstrated autopsically.

From the two statistical compilations made by Grandidier some time since, we have drawn up the following table, showing the comparative frequency of spontaneous bleedings in different parts of the body in 308 carefully described cases.

Hemorrhage from the nose	152 times.
" " gums	38 "
" " intestines	35 "
Hæmoptysis	17 "
Hæmaturia	16 "
Hæmatemesis	14 "
Hemorrhage from the female genitalia	10 "
" " tongue	6 "
" " external auditory passage	5 "
" " tips of the fingers	4 "
" " scalp	4 "
" " caruncula lacrymalis	3 "
" " ulcers of the skin	2 "
" " the upper eyelids	1 "
" " umbilicus long after healing	1 "

The above table, which of course comprises only a small fraction of the spontaneous hemorrhages that have actually occurred in bleeders, shows at least that epistaxis is by far the most frequent form.

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[1] St. Louis Med. and Surg. Journal. N. S. VII. p. 535. 1870.

[2] Gazette Médicale de Paris. 1838. p. 43.

[3] Schmidt's Jahrbücher. CLIV. S. 91.

[4] Die Haemophilie. Dissert. Berl. 1869.

As regards the *mode of escape of the blood* in the external hemorrhages of hæmophilia (both the traumatic and the non-traumatic), all the descriptions of writers agree that the bleeding takes place, as a rule, not from large vessels, but from *numerous vessels of the smallest size* (capillaries). On inspection, therefore, of the bleeding part, it has only rarely been possible to distinguish any particular vessels from which the blood was escaping in a jet or stream ; on the contrary, the extravasation has almost always been found to take place, after the manner of the so-called *parenchymatous bleedings*, from a great number of minute openings, as if from the pores of a compact sponge saturated with fluid (Wachsmuth, Grandidier, Vieli, Virchow, and others). Notwithstanding, however, the usually capillary character of these hemorrhages, the blood is poured out under a *comparatively very strong pressure*, as is shown not only by the rapidity with which a large quantity of blood is lost from even a small surface, but also by the great difficulty of checking the bleeding by means of external compression. For, usually, on every attempt to control the bleeding by pressure with the finger or a compress, the blood very soon wells up at the side, while at the same time, or generally even before this result is noticed, an extensive ecchymosis (interstitial bleeding) takes place in the surrounding parts (Buel). The danger, however, lies not so much in the force of the hemorrhage, that is, in the rapidity or *momentary profuseness* of the loss of blood, as in its *extensive duration;* in fact, it is this *obstinate persistence of every hemorrhage, whatever its origin, which is the most important and at the same time the pathognomonic peculiarity of the bleeder diathesis.* Thus, it is by no means an uncommon experience in these cases to find that an originally trifling hemorrhage, which there was every reason to expect would soon cease spontaneously or yield to treatment, still persists, in spite of all efforts to check it, not only for hours, but even for *days and weeks together*, and finally reduces the unfortunate patient to a state of extreme anæmia, or even destroys life (see Terminations). The symptoms which arise during the course of such protracted hemorrhages, and, it may be, usher in a fatal result, are naturally the same as are ordinarily met with in extreme anæmia, viz., marked decoloration of the skin

and visible parts, the facies Hippocratica, a small, soft, and finally scarcely perceptible pulse and heart-beat, a blowing systolic murmur over the heart, and usually, so long as the circulation retains a certain degree of force, a loud venous hum in the cervical veins; finally, extreme exhaustion, hallucinations, delirium, turns of faintness, and even actual syncope, in which the patient lies for some time in a condition simulating, and often terminating in death. The fatal result in these conditions of extreme prostration usually takes place with complete loss of consciousness, or with convulsions, such as occur in the anæmia produced by loss of blood under other circumstances, or else, with the symptoms of simple syncope (paralysis of the heart). On the other hand, the occurrence of syncope appears by no means infrequently to be the means of saving the life of the patient; for, after all efforts to check the hemorrhage have failed, the bleeding sometimes at last ceases of its own accord during a death-like swoon, and life is gradually restored after the patient has lain for hours or days in a sort of *vita minima*, waxy pale and unconscious. Indeed, even more remarkable than the severity of the hemorrhages are the *marked tolerance with which bleeders bear great losses of blood*, and especially the rapidity with which *restitution of the blood-mass* is usually effected even after enormous extravasations. When we consider that these losses of blood often amount to several pounds, and not infrequently recur several times at comparatively short intervals, it must certainly be a matter of surprise that a fair degree of health is in general so long preserved, or so speedily regained when temporarily lost; that in fact so many of these individuals even present a fresh, well-nourished aspect, frequently complain of flushings (see Etiology), and are at the farthest possible remove from any appearance of anæmia.

We give here a few instances in which the quantity of blood lost has been particularly noted. Thus, Coates's patient is stated to have bled three gallons (24 pounds) in eleven days, Hay's patient two quarts for several days in succession, and Smithharst's patient three pints. In Krimer's case four pounds and a half of blood were lost within twenty-four hours after the extraction of a tooth, and in Schaefer's case from three to four pounds daily for several days after the same operation. In a new-born infant, belonging to a Jewish bleeder family, Thal found

after the circumcision a quart of coagulated blood covering the parts adjacent to the wound. Uhde was informed by a patient, a man forty-four years of age, that his periodically recurring spontaneous bleedings from the nose, gums, etc., lasted, as a rule, for more than a week and until he became completely unconscious; for several days afterwards he lay in a death-like stupor, then gradually returned to life and consciousness, and convalesced, at first slowly, but afterwards, with the return of appetite, so rapidly that within a few days he again "bloomed like a rose."

With respect to the *composition of the effused blood*, numerous reports are to be found in both the earlier and more recent literature of hæmophilia, but only very few careful microscopico-chemical examinations. The pale color and watery consistence of the effused blood, mentioned by almost all writers as noticeable *during the later stages of the hemorrhage*, it should be premised, are by no means to be regarded as characteristic of the disease, for the same qualities are found also in the blood of non-bleeders as a result of the extreme anæmia following protracted hemorrhages. No correct inference, therefore, can be drawn in regard to the composition of the blood in bleeders, except from an examination of the fluid which escapes at the *beginning of the hemorrhage*, before it has undergone the typical changes belonging to acute anæmia (see Vol. XVI., p. 360). The number of exact analyses of such blood, as already remarked, is still far from large; still, the gross examinations, such as could readily be made, have been sufficiently numerous to establish conclusively at least two important points:

1. The blood in bleeders at the outset of the hemorrhage is *not paler in color than in healthy persons*, but gradually becomes so as the hemorrhages continue, in consequence of the ensuing oligæmia.

2. The blood in bleeders *maintains completely its coagulability* for a long time during the hemorrhage, and does not acquire the above mentioned watery quality until late in the attack (Buel, Stoehr, Wachsmuth, Meinel, Assmann, and others).

These results of the gross examination, pointing to the primary *absence of oligocythæmia* or *hypinosis* (deficiency of the blood in fibrinogenous and fibrinoplastic material), and probably also of a *leucocytotic* condition of the blood in bleeders, is, more-

over, supported by the few microscopical and chemical analyses that have been made (Heyland, Finger, Assmann, Gavoy-Ritter, Otto). These investigations show that the blood in hæmophilia is not only not deficient in red blood corpuscles and fibrin generators, but, on the contrary, *contains an unusually large amount of these elements*, and is, moreover, characterized by a comparative poverty in leucocytes. Such a conclusion, if confirmed by future observation, would certainly prove of great importance in reference to the theory of the disease, as demonstrating that the habitual condition of the blood in these individuals is rather one of plethora than of anæmia, and that the latter is merely a transitory accident of the disease.

Assmann (Die Hæmophilie. Inaug. Diss. Berlin, 1869) in several cases carefully counted the red and white blood corpuscles under the microscope, and always found an absolute increase of the former, the relative proportion being as much as 1,500 to 1. A similar result had previously been obtained by Finger (Schmidt's Jahrbücher. Bd. CXVII. S. 330). The excess of fibrin in the blood first effused was long ago noted by Heyland (Neue med. und chir. Zeitung. 1844. Nr. 5), who stated that he found per thousand parts 780 water, 137 coloring matter, 70 albumen, and 5 (!) fibrin. The latter figure seems suspiciously large, but an increase of fibrin has also been shown by the more recent analysis of Ritter, published by Gavoy is his dissertation (L'Hémophilie. Thèse inaug. de Strassbourg, 1861), as well as that by Otto (Ueber die Bluterkrankheit. Leipzig, 1865).

I. *Ritter.*

1,000 parts of plasma contained:

	1st Analysis.	2d Analysis.
Water	923.20	922.44
Fibrin	2.64	2.64
Albumen	73.90	74.70
Salts	0.26	0.22
	1,000.00	1,000.00

II. *Otto.*

1,000 parts of plasma contained:

Water	905.04
Fibrin	4.35 (!)
Albumen	89.54
Fat	1.82
Soluble salts	5.43
Extractives	3.82
	1,000.00

In the latter case—one of spontaneous epistaxis—a pound of the first blood lost was examined by Scherer's method. The specific gravity was 1,028, and nothing unusual was noticed in regard to the coagulation.

After the cessation or arrest of an external hemorrhage the *wound heals* by different processes, according to the nature of the injury. Clean incised wounds usually heal rapidly by first intention (Otto, Buel, Elsaesser, Schulze, Uhde); still the resulting linear cicatrix shows for a time a marked tendency to reopen, and in this case another exhausting hemorrhage generally ensues. Irregular lacerated wounds, deep excoriations, and large surface wounds, on the contrary, very rarely heal by primary cicatrization, but almost always by suppuration, during which protracted process various secondary accidents are liable to occur, such as hemorrhages from the soft, generally fungous, and extremely lacerable granulations in the base of the ulcer, retention and putrefactive decomposition of coagula of blood in the wound, secondary gangrene, etc. (Dequevauviller, Thal, Uhde, Vieli, and others). Should, however, a cicatrix be ultimately formed in spite of these obstacles, its delicacy and great vascularity will involve a much greater danger of recurrent hemorrhages than when the cicatrization has taken place by primary intention.

Interstitial bleedings.—This variety of hemorrhage in bleeders, like the preceding, may occur either *traumatically* from pressure, a blow, or bruising of the parts, or apparently *spontaneously*, *i. e.*, without any demonstrable injury. It is not improbable, however, that many of these so-called spontaneous interstitial extravasations are actually produced by mechanical injuries, which were of so trifling a nature as to have escaped attention. We have already seen that one of the chief peculiarities of the bleeder diathesis is the readiness with which trifling mechanical injuries give rise to very extensive ecchymoses, and it is not unreasonable therefore to suppose that in many of these apparently spontaneous cases we have really to deal with the effects of local injuries, the mechanical causes of which elude detection. By this remark, however, it is by no means implied that all interstitial hemorrhages in bleeders are of traumatic origin; on the contrary, there is every reason to suppose that they may

occur also, equally with the external hemorrhages, simply as a result of local congestions or of a general increase of the blood-pressure.

Interstitial hemorrhages, particularly those of an undoubtedly traumatic nature, belong in general to the earliest visible manifestations of hæmophilia, since they frequently make their appearance during the first few days of life, or even during birth, from pressure or other mechanical injury of the body of the child during the act of parturition. In after-life, besides occurring as the direct result of injuries or as the effect of an antecedent congestion and plethora, these interstitial bleedings are quite often noticed in connection with the external hemorrhages, both the traumatic and the spontaneous varieties. In this case the surface of the body very frequently becomes covered more or less universally with numerous hemorrhagic efflorescences indicative of the occurrence of *multiple* interstitial hemorrhages.

The usual *anatomical seat* of the interstitial bleedings is the *skin* and *subcutaneous connective tissue;* in very rare instances also the autopsy has demonstrated their presence in the internal structures, *e. g.*, the gastric mucous membrane and the brain (Schoenlein, Virchow). The cutaneous and subcutaneous forms, when produced *traumatically*, exhibit a special predilection for the *back*, *fundament*, the *neighborhood of the trochanter* and the *back of the neck*—in short, those parts of the body which are most subjected to pressure in consequence of the posture of the individual in sitting or lying, the wearing of tightly fitting garments, etc. The *spontaneous* interstitial extravasations, on the other hand, are observed most frequently on the *hairy scalp*, the *genitalia* (particularly the scrotum), and the *extremities;* more rarely on the trunk and face (Virchow, Grandidier).

According to the *size* and *forms* of the *cutaneous* interstitial hemorrhages or purpura-efflorescences, it is customary to distinguish the several varieties by special terms; thus, the dark, bluish-red, roundish spots of the size of the head of a pin or a linseed, are known as *petechiæ*, those of larger size and irregular shape as *ecchymoses*, and the elongated eruptions as *wheals* or *vibices*.

All of these varieties are met with in hæmophilia as local

expressions of the existing hemorrhagic diathesis, and constitute the most frequent, if not the most regular, symptoms of the disease. It is to be particularly noted, moreover, that these interstitial cutaneous hemorrhages are met with far more frequently than the external bleedings (the traumatic as well as the non-traumatic) in those interesting *rudimentary cases of hæmophilia* which are so commonly observed in bleeder circles, especially among the brothers and sisters of actual bleeders, or in the mothers of hæmophilist sons (Grandidier), and which are therefore to be regarded as manifestations of a family tendency to the disease (see p. 23). On the other hand, no one of these varieties of exanthemata is at all pathognomonic of hæmophilia, since they all occur in other forms of hemorrhagic diathesis, in scurvy, in the morbus maculosus Werlhofii, etc. (see the two following chapters), and on the other hand are occasionally, though rarely, absent in genuine hæmophilia.

As regards their mode of origin, moreover, these purpuric eruptions present certain differences, which, although by no means of an essential character, are of sufficiently frequent occurrence to deserve mention. Thus, the *larger* interstitial hemorrhages, the ecchymoses and vibices, are particularly apt to originate *traumatically;* the wheals, in fact, being very often produced by pressure from the folds of tightly fitting garments upon the underlying skin, this pressure giving rise to linear extravasations, which form, as it were, impressions or copies of the individual folds of the dress. With respect to the other modifications in shape presented by the traumatic eruptions in bleeders, we have already noted a fact which has an important bearing in this connection, viz., that the size of the extravasation is almost always disproportioned to the force of the mechanical injury, even the most trifling compressions or contusions of the skin being followed by hemorrhagic effusions of very considerable extent; hence, the hemorrhagic eruptions which are produced by *obvious* mechanical lesions are almost always of larger size and more irregular shape, and very rarely present the minute and regularly roundish form of the so-called petechiæ. In regard to the origin of the latter, which are likewise (see above) of very common occurrence in bleeders, we can only say

that they sometimes make their appearance in large numbers quite suddenly and without apparent cause; at other times they follow upon the profuse external bleedings, and in rarer instances they may be regarded as consecutive symptoms of congestive hyperæmias of the skin. While, moreover, the larger ecchymoses, whether arising either traumatically or from congestion, do not appear to be connected, as regards their histological localization in the cutaneous tissue, with any special sets of blood-vessels, the petechial bleedings, on the other hand, proceed chiefly from the close, delicate networks of capillaries, which surround the sweat-glands as well as the terminations of the hair-sheaths and sebaceous follicles, and form also the starting-points of small circumscribed interstitial hemorrhages in other hemorrhagic forms of disease.

The further course of the interstitial cutaneous hemorrhages is the same as is met with under other circumstances. The extravasated blood gradually undergoes certain typical changes: the red blood-corpuscles become deprived of their coloring matter, shrink, and finally disintegrate; a portion of the separated coloring matter is absorbed by the surrounding tissue, and the rest collects in the form of granules in the spaces between the tissue-elements, where it gradually changes in color. Corresponding to these metamorphoses in the effused blood, parallel changes of color take place in the hemorrhagic eruptions. When recent, the latter, as we have already mentioned, are of a bluish-red color; later they become greenish, then brownish, yellowish, etc., and, as a rule, a considerable time (two or three weeks) elapses before they entirely disappear from the surface of the skin.

The *interstitial bleedings* into the *subcutaneous connective tissue* are frequent, but by no means regular *complications* of the *cutaneous hemorrhages*. They are observed especially after *injuries*, but may also occur occasionally without an evidence of traumatism, apparently, therefore, spontaneously (Vieli). Clinically these subcutaneous hemorrhages are of much more serious import than the interstitial cutaneous bleedings, because the effusion of blood usually takes place far more copiously into the loose coarse meshwork of the subcutaneous con-

nective tissue than into the denser and more homogeneous corium, and because the more or less extensive and prominent *blood-tumors* or *ecchymomata* (hæmatomata), which are produced by the subcutaneous hemorrhage, often become in their turn the source of further secondary disturbances. As regards their *anatomical situation*, these blood-tumors have been noticed most frequently in the region of the *false ribs*, on the *back*, and especially on the *lower extremities, the inner surface of the thighs, popliteal region*, etc. (Allan, Meinel, Martin, Grandidier, Lemp, Virchow, and others).

In the reported cases the *size* of the tumors varied considerably; many of them were as large as a goose egg or an apple, while several instances are mentioned of enormous ecchymomata, as large as a child's head or larger, which had been produced by trifling contusions, or had apparently arisen spontaneously. The tumors, moreover, presented marked differences in *resistance*, many of them being as hard as a board, others soft and fluctuating; frequently also the hard swellings ultimately became soft and distinctly fluctuating on palpation, or, on the other hand, even increased in density. These differences probably depend for the most part upon the location of the tumors, since in general the latter are soft or even fluctuating to the feel in those situations where the subcutaneous connective tissue is of a coarser texture and readily movable, and where therefore larger quantities of fluid or loosely coagulated blood can be effused into its interstices. On the other hand, the resistance of the tumor will naturally be much greater where the tissue is denser and possesses narrow meshes. In the latter case the original induration is modified in various ways by the subsequent changes which the extravasation undergoes (see below). The *color* of the blood-tumors is usually a bluish-black; they are generally, moreover, surrounded by quite a broad, rosy halo, which is evidently the result of a reactive inflammation excited by the effused blood, as is shown by the *tenderness*, which may even increase to severe pain, especially when pus has formed underneath the skin.

A frequent *termination* of these subcutaneous hæmatomata in bleeders is in *secondary suppuration* and *ulceration* of the

infiltrated tissue. When this result occurs, the originally hard and resistant tumor becomes soft and fluctuating, usually first over its central portion ; the skin becomes thinned, and external rupture takes place either spontaneously or from some accidental or intentional traumatic lesion. The discharge is almost always composed, in addition to pus and shreds of tissue, of a large quantity of blood, and is generally followed by a very obstinate and copious external hemorrhage. The rupture or opening of a subcutaneous blood-tumor in a bleeder is evidently, therefore, always attended with risk, and at times with urgent danger. Another source of danger is the occurrence of dry gangrene of the skin covering the tumor, or of sloughing of the infiltrated connective tissue before or after the opening of the hæmatoma. In both of these conditions, especially the latter, a profuse intercurrent hemorrhage is to be apprehended from the erosion of small vessels. In many cases, on the other hand, these blood-tumors run a more favorable course : no rupture occurs from any of the previously mentioned causes, but the effused blood is gradually absorbed, and the tumor, after becoming softer, but still not fluctuating, finally disappears entirely. Still, the process of involution requires months for its completion, and during this time slight mechanical injuries not infrequently excite renewed interstitial hemorrhages, and a more or less complete restoration of the original size of the tumor.

Other symptoms of hæmophilia.—We have already described so fully the essential clinical features of the disease while considering the hæmophilia bleedings, that little is wanting to complete the picture. Aside from the existing hemorrhagic diathesis and the intercurrent constitutional disturbances produced by it, there is usually little in the general condition of these patients that is actually abnormal, or even specially characteristic. Their bodily functions, digestion, respiration, the urinary and other secretions, are frequently performed with entire regularity. Exceptions to this rule have, to be sure, been often observed, and disturbances of various kinds have been described in reference to this or that particular function ; still it seems to be entirely clear from the data we possess that these individual differences are either merely *physiological peculiarities of the constitution* such

as are met with in perfectly healthy individuals, or else, *pathological accidents*, which have no direct connection with the hæmophilia itself. The reader is referred, therefore, for whatever further information he may derive on any of these points, to the original articles (see Bibliography).

There are, however, on the part of the *organs* of circulation, certain pathological phenomena which are of such constant occurrence in this affection as to be of special significance. These symptoms, which may be briefly characterized as *congestive* or even as *plethoric*, have been already referred to in the etiology, and again just now in our consideration of the bleedings, for the reason that the abnormity in the circulation or quantity of blood which these symptoms denote is probably not without an important determining influence upon both the occurrence of the spontaneous and the course of the traumatic hemorrhages. In the chapter on the Nature of the Disease we shall consider this point more fully, but we may here add that these signs of increased arterial tension and plethora (violent beating of the heart, a full, hard arterial pulse with fulness of the visible veins, flushed appearance, sensation of heat, headache, giddiness, mental excitement) are not only observed very frequently as prodromata for some time previous to the spontaneous bleedings, but also still more frequently make their appearance and gradually disappear again without the production of hemorrhage. Such, briefly, is the part which these symptoms are observed to play in the etiology and symptomatology of hæmophilia ; the consideration of their further causal relation to certain frequent complications and sequelæ of the disease must be deferred to a later chapter.

Anatomical Changes.

The total number of autopsies made thus far upon the bodies of bleeders is perhaps as large as might have been expected in view of the comparative rarity of the disease ; still, so few of even this small number have been conducted with the necessary care and thoroughness, that it certainly seems premature at present to speak of certain patho-anatomical conditions as if they were *constant* anomalies of the bodily organization in

bleeders. The few results that have been obtained are, however, sufficiently important to deserve full consideration, especially as they seem to throw some light upon the deep obscurity which otherwise involves the nature of the entire affection (see below). Should future autopsies reveal with more and more frequency the existence of conditions similar to those to be presently described, we would then have a definite patho-anatomical basis for a rational interpretation of the clinical phenomena in many cases of hæmophilia.

It is probably scarcely necessary to show here in detail that many of the changes which have been repeatedly found at these autopsies are by no means to be regarded as anatomical causes of the bleeder diathesis, but rather merely as results or accidental complications which have no necessary connection with the disease itself. The purely accidental changes need not detain us, while as regards the simple consecutive lesions it need only be remarked, that when the death had resulted from traumatic hemorrhage, the body naturally presented traces of the wounds; furthermore, that petechiæ, ecchymoses, and blood-tumors were observed in cases which had presented these symptoms before death; and finally, that as the fatal result had in most cases been occasioned by loss of blood, there were generally to be observed the usual cadaveric signs of the intense *anæmia*, viz., extreme decoloration of all the external and internal parts, a minimal quantity of blood everywhere in the body, and a pale, watery condition of the residual blood.

No apparatus of the body seems to be abnormally affected in bleeders so uniformly as the *vascular system* (Virchow). Both the older and more recent writers speak of the *striking superficiality and abnormal distribution of the cutaneous and subcutaneous veins and arteries*, and especially of the *abnormal structure and width of the arteries* (Blagden, Schoenlein, Schliemann, Liston, Wilson, Hooper, Fischer, Virchow, Grandidier, Gavoy, Uhde, Schuenemann, ll. cc.). Thus, in quite a large series of cases, *the intima of the smaller and larger arteries* (the temporal and radial, the aorta, pulmonary, carotid, etc.) was found to be remarkably *thin*, and sometimes *actually transparent*, without any apparent diminution, however, in the elastic retractility of the coats of the vessels (Virchow); while in a certain number of these cases *the lumen of the large arteries* (aorta, pulmonary) and their main branches was *abnormally narrow* throughout the entire extent of the vessels (Schliemann, Vir-

chow, Uhde). Very generally, also, where the autopsy was carefully made, the intima of both the large and the small arteries was distinctly seen to have undergone a *partial fatty degeneration* quite analogous, as regards its locality and other characters, to the degenerative changes of the inner coat of the vessels in *anæmia* and *chlorosis* (Vol. XVI., pp. 358 and 530).

The subject is one of such great importance that it is only proper to complete the above general sketch by citing a few reports of the results found in particular cases of the disease. As early as the year 1817, Blagden, on ligating the temporal artery in a bleeder twenty-seven years of age, found that its coats were as thin as those of a vein; at the subsequent autopsy a similar condition was detected in other branches of the external carotid, and in this vessel "there were several opaque white depositions on the outer surface of its inner coat, such as precede ossification" (fatty degeneration, according to Virchow [1]). A similar condition was found by Hooper (1840) in the radial arteries, as well as in other vessels of the arm, in a bleeder twenty-five years of age, who had bled to death from a slight contused wound in this region, occasioned by a fall from a horse.—Wilson (1840) [2] found the walls of the arteries in a bleeder child three and a half years old, only half as thick as normal, and Fischer (1855) also found the coats of the arteries extremely thin and transparent in a bleeder aged eighteen. Previous to this, in 1831, Schliemann published a case observed by Schoenlein, in which the pulmonary artery of a bleeder fifteen years old was observed to have unusually thin walls and an abnormally small calibre. Narrowing of the pulmonary artery was also noticed subsequently by Gavoy (1861) at the autopsy of a bleeder fourteen years of age. Far more frequently the aorta has been found to be narrowed; at least, Virchow in his treatise on chlorosis,[3] while describing the vascular lesions of that affection, mentions also that he has met with this defect of growth in *almost all* the autopsies made by him on bleeders since 1857, when his attention was first called to it by a striking case of hæmophilia reported by Lemp—a man twenty-four years of age, with an enormous hæmatoma of the right thigh. It is probable, therefore, that this arterial hypoplasia, together with the partial fatty change which generally accompanies it, is by no means peculiar to severe forms of chlorosis, but likewise bears a specific relation to hæmophilia, of which it frequently seems to constitute the anatomical substratum.

As regards the condition of the *heart*, our information is less definite. To be sure, most of the recent reports of autopsies

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[1] l. c. p. 268.

[2] This date is incorrect. The case is related in Wilson's Lectures on the Blood, etc. London, 1819. p. 412.—TRANSLATOR'S NOTE.

[3] Ueber die Chlorose und die damit zusammenhängenden Anomalien im Gefässapparate u. s. w. Berlin, 1872.

mention a fatty degeneration of the musculature of the organ; but, in view of the extreme anæmia of the cadaver in the majority of cases, it seems to be altogether probable that the lesion in question is merely the *anæmic* form of fatty heart (see Vol. XVI., p. 358). The *size* of the heart is reported in some cases as normal (Elsaesser), more frequently as *hypertrophic;* the latter condition sometimes involving the entire organ (Gavoy), but generally only the *left ventricle* (Besserer, Schneider, Virchow). The absence, however, of any definite mention of the size of the heart in many other cases, particularly in the older reports, leaves it still doubtful whether a moderate degree of hypertrophy is a frequent or only an exceptional lesion in bleeders. Should the former prove to be the case on future investigation, the cardiac enlargement would naturally fall into line with the abnormal position and structure of the vessels as one of the determining conditions of the symptoms of hæmophilia (see later, the Nature and Pathogenesis of the disease).

As regards other organs, the lesions observed have been so various in character as to require no special mention, with the exception, perhaps, of the *spleen*, which has sometimes been found to be enlarged, softened, and engorged with blood, as compared with the other organs (Schultz, Uhde, Spahn, Buss). In the great majority of cases, however, no such changes were observed, and it is more than probable, therefore, that the enlargement of the spleen found in the instances referred to was merely an accidental complication of no importance in the genesis of the hæmophilia.

Complications and Sequelæ.

The disposition to other diseases does not appear to be essentially different in bleeders from that of healthy individuals; at least we find it mentioned in many of the reports that the patients suffered, equally with non-bleeders, from the most various acute and chronic local and general affections, which apparently stood in no genetic relation to the habitual hemorrhagic diathesis. These *accidental* complications, it is interesting to observe, do not in general seem to run a more unfavorable course

in bleeders than in others, unless the complications are of such a nature as to excite the intercurrence of hæmophilia bleedings (Grandidier). In brief, therefore, it may be said, as regards the majority of other affections, that the existence of this diathesis does not noticeably predispose to their occurrence, affords no marked immunity from them, and does not appear to materially modify their results.

Whether bleeders and their immediate non-bleeder relations are really less liable than other persons to *consumption* (Grandidier) must, in the absence of exact statistics, still remain doubtful. At all events, the immunity is not absolute, for well-authenticated cases of fatal phthisis have been reported in bleeders and their relations (Bjorkmann and Lindbeck, Finger, Lindwurm, Schmidt).

Just as all kinds of acquired morbid processes arise and run their course independently alongside of this permanent diathesis, so hæmophilia may be occasionally complicated also with other diathetic affections, which from time to time produce their characteristic derangements of health. Thus, combinations of hæmophilia with scrofula have been repeatedly observed (Schliemann, Lindwurm, Reinert, and others), and in other cases gouty attacks are mentioned; still these instances form so small a fraction of all the cases of hæmophilia, that there does not seem to be even the remotest justification for regarding these complications as anything more than mere "accidents," for which the bleeder diathesis is in no way responsible.

On the other hand, some few affections are encountered in connection with hæmophilia so regularly, or at least with such striking frequency, that we cannot but regard them as more or less dependent upon the affection in question. This is obviously the case with the *acute general anæmia* which ensues after each of the bleedings, and which, from its natural connection with the hemorrhages, might with equal propriety be classed either with the symptoms or with the complications of hæmophilia. We prefer, however, to include it under the latter head for two reasons: first, because, until the blood-mass is completely restored, the anæmia modifies the usual bodily condition of the patient so essentially as to become itself the object of separate attention and treatment; and secondly, because, upon theoretical grounds

to be considered later, it seems to us particularly desirable that the symptoms which belong to the hæmophilia *per se* should be distinguished fundamentally from those of the consecutive intercurrent anæmia.

The so-called *rheumatic affections* are also of such frequent occurrence in bleeders and their immediate relations as to deserve mention in this connection. In fact, Grandidier, while he regards these attacks as "pseudo-rheumatic" in character rather than as belonging to "true" rheumatism, mentions them among the symptoms of hæmophilia in direct connection with his description of the external and interstitial bleedings. That painful swellings of the joints, muscular pains, and also neuralgic attacks, particularly violent toothache, are of extremely common occurrence, not only in actual bleeders, but also in their non-bleeder brothers and sisters, can certainly no longer be disputed, since the number of bleeder families in which these rheumatic or pseudo-rheumatic affections occur in a cumulative manner is already quite large and is steadily increasing. To include these attacks, however, among the symptoms proper to hæmophilia, or to designate them, as Grandidier has done, by a term which distinguishes them from true "rheumatic" processes, seems to us at present of doubtful propriety, for the reason that they are met with in only a minority of cases, and moreover are identical, so far as their mode of occurrence and general course is concerned, with the ordinary forms of rheumatism. For these reasons we have preferred to consider them among the complications of hæmophilia, and to regard them as an indirect rather than as a direct effect of hæmophilia, leaving to the future the determination of the real nature of the causal nexus.

As far as we can ascertain, rheumatic affections of the above general character have thus far been observed in the members of eighty-two bleeder families. This number, although quite large, is still too small in comparison with the total number of bleeder families to warrant us in regarding these attacks as immediately dependent upon the bleeder diathesis.

The most important of these rheumatic diseases in bleeders are unquestionably the *joint affections*. These comprise all grades of arthritic rheumatism, from simple inflammatory arthralgia up

to the most copious synovial effusions. The attacks appear to occur most frequently during the cold, damp weather of spring and autumn (Vieli, Grandidier); sometimes they are preceded, like the spontaneous bleedings, by various symptoms of congestion; at other times they occur without any prodroma whatever. Their relation in point of time to the bleedings is by no means typical, since they may precede, accompany, or follow the latter. In many cases their development is quite acute, at other times slower and more gradual; in the former case febrile symptoms usually occur in addition to the articular pains, in the latter there is usually an absence of fever. The course of those attacks, in which the pain is a more prominent symptom than the effusion, resembles, or is identical with, that of so-called acute articular rheumatism. Thus, in many of the cases the pains occur in several joints simultaneously, alternately decline and increase again in intensity, or migrate from one joint to another. Sometimes, however, the pain is confined for some time to a single joint, which in certain cases may also present the signs of fluid effusion. These effusions are usually serous, but it is probable that they may also be sometimes of a sanguinolent character, at least it is so stated by Dubois, Camman, and Assmann. In the latter case the effusion is clearly to be regarded as a direct symptom of the hæmophilia, in the same sense as the internal superficial hemorrhages of bleeders. Whether extravasations of blood ever take place into the cavities of the joints in these patients cannot be determined with certainty in the absence of any autopsical results upon this point. In the reported cases of this kind the diagnosis has rested merely upon clinical symptoms, such as the greater painfulness of the swollen joint, the pressure of cutaneous hemorrhages in the neighborhood, and the palpatory evidence of solid masses in the fluid effusion, which were supposed to be coagula of blood. Still, these cases have been decidedly exceptional; far more frequently the symptoms have all pointed simply to a serous effusion, viz., more or less swelling of the joints, *moderate* pain on forcible pressure, or even an entire absence of pain, and usually on careful exploration the evidence of fluctuation.

The termination of most of the reported cases has been in

recovery, with a gradual or rapid subsidence of the pains in the painful forms, or with absorption of the fluid effusion in the exudative affections of the joints. In many of the latter cases the attack appeared to be followed by considerable thickening of the synovial membrane, as well as by thickening and shortening of the accessory ligaments, resulting in permanent anchylosis. This unfortunate result was noticed most frequently in the knee, but exceptionally also in other joints (elbow, hip). Suppuration of the joints, on the other hand, has never been observed in these affections as a result of the inflammatory process.

The *rheumatic muscular affections* in bleeders completely resembled, in their clinical features, the ordinary forms of rheumatic myalgia. They occurred still more frequently than the joint affection, and very often were superadded to the latter. As regards its mode of occurrence, duration, and localization, the muscular affection was far from presenting any uniform or typical character; on the contrary, the greatest diversity in these respects was observed in the individual cases. The usual termination was in recovery, *i. e.*, disappearance of the pain and complete restoration of function; in some instances, however, probably in consequence of proliferation of the interstitial connective tissue and subsequent contraction of the latter, the chronic rheumatic myositis finally resulted in permanent contracture and consecutive atrophy of the affected muscle.

The *neuralgic attacks* of bleeders seem to affect most frequently the *dental branches of the trigeminus*. Thus, Grandidier mentions the striking frequency with which bleeders suffer from periodic attacks of violent toothache, often independently of any obvious cause such as caries. As experience has amply proved, there is great risk in these cases that the patient, in spite of all warnings, will insist upon the extraction of one or more teeth, an operation which is followed usually by dangerous, and sometimes by actually fatal hemorrhage from the lacerated vessels of the alveoli.

In concluding our consideration of the complications of hæmophilia, it may be added that the rheumatic disposition not only occasionally *outlasts* the tendency to hemorrhages, but in some

instances does not make its appearance until after the extinction of the latter, and then is entitled to be regarded rather as a *sequel* than a complication of the disease (see Duration, Termination, and Prognosis). Little is known in regard to other sequelæ, partly because many bleeders die at a very early age from the direct effects of the disease, partly also because the affection in others persists into old age, and finally because the number of complete and incomplete cures of the bleeder disposition, notwithstanding all the cases that have been reported, is still comparatively small. We merely remark, therefore, that besides the purely accidental affections noticed in these persons after the subsidence of the hemorrhagic disposition, in some cases moist eruptions on the head, and in others hemorrhoids, are mentioned as making their appearance so immediately after the disappearance of the hæmophilia, that some observers have preferred to regard these complaints as *critical* manifestations of the disease, or perhaps even as anomalous symptoms of a still existing, but latent, bleeder diathesis.

Nature and Pathogenesis of Hæmophilia.

In the foregoing remarks on the etiology, symptoms, anatomical changes and more important complications of hæmophilia, we have endeavored to present the reader with a brief account of the known facts so far as they are externally related to each other; the question now naturally arises, what is the causal nexus between these empirically ascertained facts, or, in other words, how are we to interpret the *nature* and *pathogenesis* of this remarkable affection? At the very outset of this article we were obliged to confess that all the hypotheses and theories advanced hitherto in reference to the nature of the bleeder disease—even the most recent and best established of them not excepted—are still very defective, and by no means suffice to bring the observed symptoms into complete accord with the post-mortem results and etiological facts. But none of these hypotheses fail so completely to meet the requirements of modern pathology as those which, without attempting to account for the clinical and anatomical facts of the disease, and without any evidence but a fancied

resemblance, simply assert the relationship or even identity of hæmophilia with other more or less imperfectly understood constitutional anomalies.

To this category belong some of the older views of the affection, which have long since been abandoned, and now possess merely an historical interest. According to these, hæmophilia was supposed to be, properly speaking, not an independent disease, but merely an exceptional expression of morbid bodily conditions, which ordinarily manifested themselves under other and what might be regarded their legitimate clinical forms. Thus, Krimer assumed that hæmophilia is identical in its nature with the congenital *arthritic* dyscrasia, of which he supposed it to constitute merely a special variety; while, on the other hand, Schliemann regarded it as a particular modification of scrofula. These hypotheses were based simply upon the observation of cases in which bleeders had suffered from gouty attacks later in life, or had presented symptoms of scrofula in addition to those of hæmophilia, without there being any plausible reason whatever for inferring an essential connection between the two classes of symptoms, and in spite, moreover, of the well-known fact that the majority of bleeders do not suffer from gout or scrofula, and that the majority of gouty and scrofulous individuals are not subjects of hæmophilia. Still more arbitrary was the assumption of Heyfelder, who united these two opposing doctrines into a single theory, according to which the underlying constitutional anomaly of hæmophilia was held to be a *combination* of hereditary arthritis and scrofula. This view, which we have mentioned merely for the sake of completeness, may be left to the refutation which a simple statement carries with it.

Far more plausible is the view entertained by some other writers (Vieli, Grandidier, Hyde-Salter, et al.), that there is a close relationship between hæmophilia and the *rheumatic* disposition. This opinion was based upon certain facts, to which we have already alluded in the preceding chapter, viz., that a very large proportion of all the hitherto observed cases of hæmophilia suffered at some period of their lives, either during the continuance of the hemorrhagic diathesis or after its disappear-

ance, from so-called rheumatic attacks (painful affections of the joints, muscles, etc.), and that, furthermore, the same symptoms have been noticed also to occur in a strikingly cumulative manner within the circle of many bleeder families. Were the question merely one of relationship, and not of identity, between the two forms of disease, the above view might be accepted without much hesitation, since there can be no question that bleeders as a class exhibit a marked predisposition to rheumatic affections. But we fail to see any good reason for regarding hæmophilia as simply a special form of rheumatism. In the first place, rheumatism in both its hereditary and acquired form is far more frequently met with clinically as an entirely independent disease wholly unconnected with hæmophilia, and, therefore, in all probability rests upon a much wider etiological basis than does the latter affection. Furthermore, the rheumatic affections in question are by no means universal in bleeders, nor is rheumatism common to all bleeder families; it seems fair to conclude, therefore, that the two pathological territories are not only unequal in extent, but overlie each other so partially that there is no warrant for their fusion into a common domain. Still, even if we restrict ourselves to the view which appears upon the whole to accord best with clinical experience, viz., that the connection between the two affections is merely that of family relationship, manifesting itself in the fact that the fundamental structural vice of hæmophilia operates also as a predisposing factor for the development of rheumatic processes, we gain very little after all towards a comprehension of the nature of the bleeder disease, so long as the nature of rheumatism is itself so imperfectly understood. While we admit, therefore, that the frequent coincidence of rheumatic symptoms with hæmophilia is a fact of great clinical interest, and may possibly help us at some future day to a correct understanding of the nature of both diseases, we fully agree with Virchow[1] in his warning against the folly of attempting to explain one unknown subject by means of another equally obscure.

The marked hemorrhagic character of the symptoms of hæmo-

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[1] l. c. p. 269.

philia has naturally led also to various attempts to connect the disease with *other forms of the hemorrhagic diathesis.* Thus, J. Vogel has maintained the identity of hæmophilia with scorbutus;[1] while Virchow at one time insisted that hæmophilia might possibly be closely related to chronic splenic cachexia,[2] but latterly seems to have entirely abandoned this opinion. If hæmophilia, however, as we had occasion to point out at the very beginning of this article, can properly be made to include only the congenital and habitual cases of hemorrhagic diathesis, together with such briefer and more tardy forms of hemorrhagic disease as are clearly connected genealogically with undoubted bleeder cases, then certainly the view which associates hæmophilia with other hemorrhagic affections must be regarded as absolutely untenable. In confirmation of this view we may note also the important fact that the severe general cachexia, which scorbutic patients present in addition to their hemorrhagic diathesis, and which is noticed also in those splenic affections during the course of which a tendency to bleedings is developed, is entirely foreign to hæmophilia *per se;* in fact, it is just the contrast between the general good health and the existing disposition to dangerous hemorrhages which is one of the chief characteristics of bleeders. Finally, the theory of a close relationship between hæmophilia and the hemorrhagic splenic cachexia is disproved by the circumstance that while the spleen has been found somewhat enlarged at a few autopsies of bleeders, in the great majority of instances no mention is made of any tumor of the organ.

The attempts to trace the origin of hæmophilia to the spleen were evidently determined by two considerations: on the one hand, by the recognized fact that this organ is intimately connected with the formation of the blood, and on the other, by the belief that the nature of hæmophilia consists in a *defective composition of the blood.* Before Virchow gave to this belief a somewhat more concrete expression by pointing out the possibly splenic origin of the supposed alteration of the blood, a variety of views as to the nature of this defect were entertained by the older writers. Thus, some supposed it to consist in a *retention*

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[1] Handbuch zur Kenntniss und Heilung der Blutflüsse.

[2] l. c. p. 269.

of the blood at its embryonic stage of development (Meckel), and others in a *deficiency of fibrin and red blood corpuscles* (hypinosis and oligocythæmia rubra).[1] The untenableness of these theories, however, ultimately became apparent, when it was proved by Wachsmuth, Besserer, Meinel, and others, that the blood in bleeders is by no means defective either in its organization or composition, and that when care is taken to collect and test the first blood which flows, the latter is found to coagulate readily and to be no lighter in color than usual. The careful microscopic and chemical analyses made still more recently (see p. 45), all show conclusively that the blood in hæmophilia actually contains more than its normal share of fibrin and red blood corpuscles, and in other respects completely resembles normal blood; so that, for the present at least, the hypothesis that the bleeder disease is in general dependent upon a congenital imperfection of the blood, or is a dyscrasic affection, will have to be entirely abandoned.

In thus rejecting all dyscrasic theories of hæmophilia, we by no means wish to be understood, however, as denying the occurrence of *accidental* changes in the blood, but only as insisting that these are to be considered merely as casual complications, or as *consecutive* disorders incident to the disease. Under the latter head we have in mind particularly the very *intense acute oligæmia* which so frequently develops *intercurrently* as a necessary result of the hemorrhages, and which, should the hemorrhage prove fatal, is encountered at the autopsy along with the other consecutive lesions. That this purely *secondary* alteration of the blood can in no wise be held responsible for the morbid disposition—the *primary* disease—is so perfectly obvious that this renewed allusion to the subject might seem entirely superfluous; still we deem it necessary to again call attention to it expressly, because this secondary oligæmia of bleeders, like every other intense oligæmia, determines in its turn, through a sort of vicious circle, the production of conditions which not only protract the *continuance* of the immediately *existing* hemorrhage, but also in a special manner favor the occurrence

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[1] *Nasse, Elsaesser*, and others.

of *new hemorrhages* in other localities. For, the more watery (hypinotic) the blood becomes in consequence of the progressive loss of blood, the more unfavorable will evidently be the conditions for the spontaneous arrest of the external hemorrhages by the formation of a clot upon the bleeding surface. Furthermore, the greater the diminution in the stock of the red blood corpuscles, the greater the danger of the development of a *secondary hemorrhagic diathesis*, induced by the *defective functional restitution and impaired nutrition of the walls of the vessels* (see the articles on Anæmia, Chlorosis, and Progressive Pernicious Anæmia, in Vol. XVI., particularly pp. 358, 530, 585). In this way the temporary oligæmia occasioned by loss of blood, besides materially promoting the persistence of the *primary* bleeding, in all probability also determines the occurrence of those *secondary* hemorrhages, which, in the form of petechial superficial hemorrhages from mucous membranes, etc., so frequently accompany or follow the true (primary) bleedings of hæmophilia.—Strictly speaking, therefore, it does not seem to us quite correct to regard these secondary hemorrhages as *hæmophilia* bleedings, notwithstanding the fact that they occur in bleeders, and are, equally with the primary bleedings, the expression of a hemorrhagic diathesis ; on the contrary, they appear to be completely analogous to the hemorrhagic attacks which occur also in non-bleeders as a result of intense oligocythæmia from any cause, and are therefore to be regarded as merely the clinical manifestations of a *transitory* disposition to hemorrhages only very indirectly connected genetically with the congenital and habitual hemorrhagic diathesis of hæmophilia.

Besides the above-mentioned secondary hemorrhagic diathesis, we certainly ought to include also, among the results of the symptomatic oligæmia of bleeders, the degenerative changes so frequently found at the autopsy in the muscular substance of the heart, the intima of the vessels, etc., because exactly the same lesions are constantly met with in other cases of intense anæmia, particularly in those of a progressive pernicious character (see the articles referred to above), and are obviously, therefore. not directly due to the hæmophilia itself. To attach importance to these probably often quite terminal degenerations, in connection with the occurrence of the *primary* bleedings, as if the vascular degeneration had been an original and continuously acting predisposing cause of rupture of the vessels, seems

to us therefore highly objectionable. Indeed, it is at once clear, from the very nature of hæmophilia as a congenital and persistent hemorrhagic diathesis, that the underlying anatomical cause must itself also possess the character of a preformed and at the same time stationary anomaly.

But what now is this enigmatic pathological something which is to be regarded as the true cause of the bleeder anomaly, and of which we have thus far been able to predicate only that it is probably not of a dyscrasic nature? Is hæmophilia at all a *patho-anatomical unit*, in the sense that invariably, in every individual case of the disease, an anatomical abnormity recurring in a stereotyped form can be demonstrated, which is capable of explaining the congenital and habitual hemorrhagic diathesis of the persons affected by it? We have already intimated repeatedly that this does *not* appear to be the case; that, at least so far as our knowledge extends at present, hæmophilia is not yet to be regarded as an anatomical, but merely a *clinical pathological unit*, because a comparison of the total autopsical results shows that there is no single anatomical characteristic common to all the cases; that, in fact, even the changes most uniformly encountered are in some instances entirely absent. Any attempt, therefore, to explain the nature of hæmophilia upon the hypothesis that all cases of the disease are anatomically identical, in the same sense as all cases of croupous pneumonia, typhoid fever, etc., are supposed to be identical, will, in our opinion, necessarily prove a failure, so that all that can be attempted at present is to apply the positive results in particular autopsies to the interpretation of the hæmophilia *in concreto*.

By far the most readily susceptible of at least a partial, if not a complete, explanation of the clinical complex of symptoms, is that entire class of cases of congenital and habitual hemorrhagic diathesis, in which the autopsy has revealed the existence of *anomalies in the position of the cutaneous and subcutaneous vessels*, particularly an *unusually superficial course of the same*, as well as certain, probably equally congenital, *structural changes in the arteries*, especially a *striking delicacy of their walls* and an *abnormal narrowness of their lumina*. Moreover, the recent observations of Virchow have shown that

in all probability this class or group includes by far the majority of cases of the disease, so that, if we are able to give some sort of anatomical explanation of the bleeder diathesis in these cases, we shall have taken an important step forward upon this difficult ground. In fact, Virchow, whose earlier but recently abandoned views have been referred to above, is now inclined to maintain a leading rôle for these vascular anomalies in the production of the symptoms of hæmophilia, and in his discussion of the similar lesions occurring in *chlorotic* individuals has attempted incidentally, and, of course, only in brief outlines, to sketch a *mechanical* explanation of the bleeder disease upon this basis. In the following brief presentation of the subject it will be our object to describe somewhat more fully the influence of these vascular abnormities upon the conditions of the circulation, and to throw what light we can upon the manner in which the lesions in question predispose to the occurrence of the bleedings of hæmophilia. At the same time, however, it should be premised that the views advanced here apply only to a certain proportion of all the cases of hæmophilia, *i. e.*, only to those in which the vascular anomalies actually exist, and that even for these cases the explanation is incomplete. In order to account fully for the clinical facts, we are compelled therefore to call in the aid of further *auxiliary conditions*, which cannot, it is true, be demonstrated with the same precision as the vascular anomalies, but may yet be inferred with the highest degree of probability from certain symptoms during life. These auxiliary conditions, the *diverse* character of which renders their existence in individual cases for the present merely conjectural, will also require to be considered in some detail, partly for the purpose of filling up logically the numerous gaps which the vascular theory still leaves in the explanation of the above cases, and partly because instances repeatedly occur in which, *on account of the absence of demonstrable vascular anomalies*, these supplementary conditions are our sole guide to the elucidation of the affection.

Before entering upon the subject of the auxiliary conditions, let us first consider the influence of the vascular anomalies themselves, and inquire in what manner *each of them, considered by itself*, promotes the occurrence of the bleedings of hæmophilia.

Now, the most important clinical features by which these hemorrhages are characterized, it will be remembered, are:

1. The readiness with which they are excited.
2. The force with which the blood escapes.
3. Their protracted duration and obstinacy.

The question before us, therefore, is how far can *the superficial position*, *the delicacy and the narrow lumina of the vessels*, favor the occurrence of hemorrhages in general, and how far can they, in an already existing hemorrhage, give it an unusually violent and obstinate character?

Now, in the first place, a *superficial position* of the cutaneous and subcutaneous vessels evidently exposes the latter more intensely and more frequently to all kinds of mechanical injuries, and therefore undoubtedly predisposes to the occurrence of both superficial and interstitial *traumatic* hemorrhages in all individuals affected with this topographico-anatomical anomaly. The same result may be brought about also by means of the *fluxions*, which the anomaly facilitates to a high degree in the capillaries of the general integuments of the body (the skin and subcutaneous connective tissue). For a diminished thickness of these tissues not only exposes the superficial arteries in an exceptional degree to all those numerous *external* influences which are known to be capable of inducing arterial hyperæmia (*e. g.*, mechanical, chemical, thermal influences, etc.), but it also opposes a lessened resistance to the expansion of the vessels by the forcible entrance of blood in fluxions from *internal* causes (*e. g.*, plethora sanguinis, violent action of the heart, etc.). But whenever such a determination of blood takes place in the superficial arteries, an overdistension and increased blood-pressure must necessarily arise also in the capillaries, and thus predispose not only to extravasations in general, but especially also to those of an unusually profuse and protracted character.

In a similar manner the *thinness of the walls of the arterial vessels* also predisposes to hemorrhagic attacks in general, and to a more malign course of the same in particular. Not only does this delicacy of structure facilitate the occurrence of traumatic lesions in the superficial arteries from external injuries, but more especially it also increases the liability to active congestions from

both external and internal causes. With the same distending force a thin arterial wall will naturally expand more considerably than a thick one, and consequently equally energetic contractions of the heart will be more likely to produce an engorgement in a vascular apparatus provided with thin walls as a result of the diminished resistance to the circulation, than in vessels more solidly constructed. The immediate result of such a distension of the arteries, provided the coats of the vessels retain their elasticity, will evidently be to propel the blood more forcibly into the capillaries in direct proportion to the arterial expansion by the systolic blood-waves. Now, at most of the autopsies of bleeders the arteries, even the largest, such as the pulmonary artery and aorta, have been found to present just these characteristics, viz., an abnormal thinness, together with a considerable degree of elasticity of the walls (Virchow), and it is fair therefore to conclude that during the life of these cases the entire capillary blood was at all times subjected to a comparatively high pressure, which might not only have favored the occurrence of hemorrhagic attacks, but also at the same time have impressed upon the latter the special character of *hæmophilia* bleedings.

As regards, finally, the influence which an *abnormal narrowness of the large arteries*, particularly the aorta, exerts upon the circulation, we may conveniently refer to our exposition of the subject in the article on Chlorosis (Vol. XVI., p. 539), where the subject was discussed at some length on account of the very important part which this particular anatomical anomaly (in connection with an increased delicacy of the arterial walls) plays also in the latter affection. The reader of that article will remember that while the clinical picture of arterial hypoplasia varies considerably in different individuals, according to the quantity of blood and the degree of elastic retractility possessed by the coats of the arteries, the anomaly in question, under some circumstances and in a certain proportion of the cases, presents the character of a *fluxionary diathesis with a tendency to profuse hemorrhages*. This will be the case particularly when, in addition to a retention by the vessels of their natural elasticity, there is also an *excessive volume of blood in comparison with the diminished*

width of the arterial apparatus (Virchow). Now, just as the *menorrhagic* type of many cases of chlorosis, as distinguished from the more common amenorrhœic form, may probably be accounted for by such a so-called *plethora ad vasa* (or plethora ad spatium), so also a sort of explanation would be afforded for the occurrence of hæmophilia bleedings and for the existence of a more or less *permanent hemorrhagic diathesis* in certain individuals with a narrow arterial apparatus, if it could be shown with sufficient certainty that the *blood-supply in these persons is habitually in excess of the capacity of the vessels!*

A *direct* estimation of the volume of blood in bleeders during life has never been attempted, and is of course impracticable; while, as we have seen, the amount of blood found after death is usually no guide as to the quantity present during life.

Although it is impossible, therefore, to prove directly (by measurement of the volume of blood) that a condition of *plethora ad vasa* exists in many or all cases of hæmophilia, still some of the clinical symptoms, it seems to us, point clearly to the great plausibility of such an hypothesis. Of these clinical indications we need enumerate only: 1. the peculiar *congestive* symptoms which so frequently precede by a shorter or longer time the spontaneous bleedings in these individuals, and which may very reasonably be interpreted as a sign of vascular engorgement; 2. the surprising *toleration* of excessive losses of blood; and 3. the equally remarkable complete and rapid *restitution* of the volume of blood. Indeed, if we examine the second and third points somewhat more closely, we find that in many cases of hæmophilia we have to deal not merely with a relative plethora (plethora ad vasa), but probably even with an *absolute plethora, which enables these individuals to bear their apparently excessive losses so comparatively well just because it is itself the expression of an unusually active power of generating blood.*

Our course of thought thus far has imperceptibly led us, as the reader sees, away from the consideration of the vascular anomalies and their effects upon the circulation, to the discussion of a *second* factor, which may possibly be of the highest importance in the production of the bleedings of hæmophilia—a factor, moreover, which is not dependent upon the configuration of the

vessels, but is ultimately connected with the *absolute quantity of the habitual supply of blood. The greater this habitual supply and the more the vascular apparatus is permanently overfilled in consequence of it, the more readily the clinical symptoms peculiar to the bleeder disease may arise*, and the greater will be the *tendency, not merely to hemorrhages in general, but particularly to those of a profuse and difficultly controllable character.* This being the case, it may readily be conceived that in certain instances the habitual existence of a *high degree of absolute plethora* may of itself be sufficient to maintain a bleeder disposition without the intervention of the vascular anomalies above described. Or, in other words, we may suppose that although in *moderate degrees of habitual plethora* hæmophilia requires for its development the concurrence of other favoring conditions on the part of the vessels (particularly *delicacy* of their walls, *narrowness* of the lumina), still the affection may now and then manifest itself as a *clinical* form of disease entirely unconnected with the vascular lesions referred to.

Such an hypothesis would not only afford a sort of explanation for that *minority of cases* in which nothing abnormal could be detected in the position and structure of the vessels, but would also serve to account for many of the characteristic features of the *more frequent* cases in which the vascular anomalies were actually present. Evidently the introduction of this second factor—*variations in the volume of blood*—would be only a gain to the vascular theory of hæmophilia, by bringing it into more complete accord with the facts, and by enabling us, without detracting from the essentially permanent character of the disease, to dispense with the conception of hæmophilia as an anomaly incapable of fluctuation. Such a conception, however, is a logical necessity so long as we regard the hæmophilia in these cases as depending *solely* upon the vascular hypoplasia, whereas in reality experience shows that the disposition of bleeders to hemorrhages, and the severity of the bleedings, are usually by no means the same at all times of life, but present all sorts of fluctuations which manifestly point to a varying intensity of certain causal factors. A vascular theory, moreover, which regards merely the position and structure of the vessels, without

taking into account also the fluid contents of the latter, would wholly fail to explain why in many cases the first visible outbreak of the bleeder diathesis, instead of occurring as usual in early childhood, is postponed to a somewhat later period of life; or why, on the other hand, the affection still more frequently declines in intensity with the advance of age, and, indeed, ultimately disappears entirely. But all these fluctuations and differences in respect to the beginning, course, and termination of the disease at once become more intelligible the moment we recognize in the *varying quantity of blood in bleeders a possible*, if not a *probable cause of variations in the disposition to hemorrhages.* Furthermore, just as there may be clinical cases of hæmophilia in which the hemorrhagic diathesis is induced and maintained simply by an unusually high degree of habitual absolute plethora *without any abnormity on the part of the vessels* (see above), so also, on the other hand, it is to be noted particularly that *even when these vascular anomalies are present, the symptoms of hæmophilia need not be invariably manifested.* Thus, these symptoms will presumably be absent, if along with the diminished capacity and imperfect development of the vascular apparatus there is also a corresponding diminution in the habitual volume of the blood, so that there is no habitual *plethora ad vasa*, no excessive distension of the thinned and narrowed, but still elastic arteries, by the systolic blood-wave. So long as the harmony between the quantity of blood and the capacity of the vessels is not materially disturbed, the hæmophilia, *although it exists in the germ on the part of the vessels*, will still remain *latent*, and may possibly continue so for the entire lifetime; but, should conditions arise which determine a temporary or permanent increase in the mass of blood, then the congenitally established hæmophilia awakens, and a transitory or persistent hemorrhagic diathesis develops, the intensity of which will depend chiefly on the degree of disproportion which now exists between the calibre of the vessels and the volume of blood.

We come now, finally, to the question whether, besides the two conditions mentioned, there may not be still other auxiliary factors concerned in the production of hæmophilia bleedings, either on the part of the bodily organization or on the part of the

vital processes of bleeders? To this question, if it be understood as applying to all cases of the disease without exception, we are by no means prepared to reply either negatively or still less affirmatively. For *certain* cases, however, the existence of such further predisposing factors may be conceded. In the first place, we may regard in this light the *habitually forcible contractions of the heart*, of which we have ample evidence in the unusually hard pulse and apex-beat of many hæmophilist individuals, and particularly in the *cardiac hypertrophy* occasionally found at their autopsies. That such a functional hyperkinesis, and especially an actual hypertrophy of the heart, will favor the formation of a congestive diathesis, and thereby predispose to profuse hemorrhages, is too evident to require detailed proof; but, besides this, the conditions in question, as they are both repeatedly observed in bleeders, afford additional support to the theory of the actual existence in these very patients of a condition of relative or even absolute habitual plethora during life. For experience shows that permanent hyperkinesis and hypertrophy of the heart are developed the more readily, the greater the quantity of blood in comparison with the obstructions to its movement in the circulatory apparatus. Some writers, on the other hand, interpret the motor excitation of the heart so frequently met with in bleeders, and also the increased thickness of the cardiac walls, as results induced by the increased richness of the blood in red corpuscles (Assmann), by means of which the heart is constantly kept in a state of increased functional as well as nutritive activity. Which of these two explanations is the correct one, or whether both factors act in combination, we shall not attempt to decide.—Some other writers, finally, have preferred to regard hæmophilia as due to a *deranged innervation of the vessels*. According to this view it is maintained that the bleeder diathesis, as well as the tendency of bleeders to *rheumatic* affections (see Complications), are in the main vaso-motor phenomena connected with an unusual disposition in certain individuals to a neurotic relaxation of the vessels, which manifests itself in frequent capillary hyperæmias, stases, spontaneous hemorrhages, and, when a wound has been received, in imperfect contraction of the vessels (Otto, Reinert, etc.). Undoubtedly this theory

also has its claims as explaining in part the origin and course of *many* hæmophilia bleedings, since the circulation is evidently influenced to some extent by the innervation of the vessels, and therefore a tendency to active neurotic dilatations of the vessels must *à priori* be regarded as contributing to the occurrence of hemorrhages of a bleeder character. Still, in view of the anatomical and clinical facts previously mentioned, which permit within certain limits a grossly mechanical view of the clinical problem, there can be no propriety whatever, it seems to us, in advancing a vaso-motor theory of hæmophilia in so exclusive a form as has been advocated by many writers, *i. e.*, as a general theory applicable to all cases of the disease. We cannot but regard it as a questionable practice, when writers, instead of directing their attention to the more immediate and more palpable causes of disease, forthwith betake themselves for an explanation to the domain of the "nervous," that "sphere of pure dynamics" to which recourse should be had only when no interpretation of the clinical facts can be found elsewhere.

Restated in a succinct form, our present knowledge of the nature of hæmophilia is probably fairly represented in the following conclusions:

Hæmophilia is, in general, a congenital and habitual form of the hemorrhagic diathesis, in which the frequently recurring and readily induced hemorrhages probably, in most cases, owe their extraordinary vehemence, obstinacy, and danger to an equally congenital and habitual disproportion between the volume of blood and the capacity of the vascular apparatus, resulting in an abnormal increase of the lateral pressure within the vessels. In many instances, moreover, functional erethism of the heart and hypertrophy of the cardiac musculature, by inducing a tendency to congestions, also aid to an important degree in producing the hemorrhages, and in giving them their abnormal clinical character. Finally, neurotic influences may perhaps occasionlly act as an additional factor by temporarily increasing the permanent congestive diathesis.

Of the three factors mentioned in the above definition, we regard the *first*—the congenital disproportion between the volume of blood and the calibre of the vessels, or, at least the existence

of a congenital *foundation* for such a disproportion—as by far the most important and most essential pathological element of hæmophilia. While, moreover, this disposition may obviously be brought about in *various* ways (sometimes *solely* by a hyperplasia of the blood, sometimes *solely* by a hypoplasia of the vessels, and sometimes by *both* anomalies combined), and while, therefore, *there is in all probability no absolutely single pathogenesis for all cases of hæmophilia*, we are still of the opinion that at least most of the cases have a similar, and, indeed, *complex* mode of origin, as is shown by the fact that in most cases there are anatomical and clinical indications of the existence of both a vascular hypoplasia and an actual, not merely a relative, plethora. Upon this view, therefore, the majority of cases of hæmophilia would probably arise in this wise, that in consequence of either hereditary or merely accidental influences operating in the original development of the body, the plastic force inherent in a certain tissue system (the vessels) is abnormally feeble, so that the evolution of the vascular apparatus, particularly the arteries, takes place incompletely; while at the same time the blood, which is so closely related histogenetically to the vascular apparatus,[1] takes no part in this defect of nutrition, but, on the contrary, grows in a normal—in fact, an excessive manner, and this tendency, moreover, is maintained throughout life. Still, it must be admitted that *à priori* a parallelism in the growth of the vessels and blood is much rather to be expected than this contrast, which in our opinion constitutes the pathological substratum of most cases of hæmophilia; indeed, this very presumption serves to explain why hæmophilia is upon the whole so *rare* an anomaly, especially in comparison with the chlorosis of congenital origin. If, however, the growth of these two varieties of tissue during the embryonic development of the individual, instead of taking place harmoniously as usual, actually proceeds disharmoniously so as to lead to the formation of the above mentioned complex defect in the original design, a further propagation of this vice by means of *hereditary transmission* in the future is, according to all analogy, not only

[1] See article on Chlorosis. Vol. XVI. p. 547.

possible, but even highly probable, so that after hæmophilia has once arisen congenitally within a given family circle, the subsequent *hereditary character* of the disease follows naturally as simply a special application of the general law of heredity. Moreover, since the transmission of hæmophilia takes place far more commonly in the *cognatic* direction, we might suppose in particular also that the *maternal* predominates over the male influence in the development of the vessels and blood; nor is there anything at all unreasonable in this hypothesis in view of the known relations of the so-called parablastic tissue (His) to the maternal organism (ovule and follicle). Furthermore, in order to account for the remarkable fact that, although hæmophilia is almost always transmitted by the mother rather than by the father, the disease in reality manifests itself by a decided preference only in the male descendants (sons), we must be able to show either that the natural disposition to vascular hypoplasia or to plethora is stronger in the male sex, or that the female sex enjoys a relative immunity from one or the other anomaly of growth. Now, patho-anatomical experience teaches most positively that hypoplasia of the vessels is by no means limited especially to the male sex, but occurs more frequently in females (see Chlorosis); on the other hand, the male organism, as is well known, is from the beginning distinguished from the female by a greater supply of blood, a more active hæmatopoiesis, and a more vigorous development of the cardiac muscle; and for these very reasons possesses, therefore, a much stronger disposition to absolute, as well as relative plethora, and at the same time, we may suppose, to hæmophilia. It seems to us, therefore, in a high degree probable that when the hereditary hypoplasia is present in the male members of a bleeder family, and becomes, in connection with a plethoric condition of the blood-mass, the patho-anatomical substratum of a pronounced bleeder affection, the same hypoplasia may be supposed to exist also in the female members; but that the latter do not themselves become bleeders simply because the bleeder diathesis is kept latent by certain normal attributes peculiar to the female organism, particularly by the smaller quantity of blood and the more feeble development of the cardiac musculature. In order to settle this point,

however, it would obviously be necessary to ascertain definitely by careful post-mortem examinations *whether the same hypoplasia which is met with in the marked bleeders of a family is also present in the bodies of their non-bleeder mothers, sisters, and brothers.* The decision of this question has never been seriously attempted, so far as we know, by any physician who has had the professional care of bleeder families, because hitherto the whole interest in regard to the morbid anatomy of the disease has been confined to the actual bleeders without extending also to the non-bleeder (usually female) members of these families. Perhaps, however, the hypothesis which we have advanced may serve to direct the attention of the medical public to this subject, and it is solely with this view that we have treated it somewhat more fully than would otherwise befit the dogmatic tone required of a work of this kind.

There is still another circumstance, moreover, which somewhat modifies the effect of an hereditary and congenital vascular hypoplasia in the female organism, *at least during the period of menstrual life*, as compared with the male. Thus, the *menstrual bleedings* unquestionably act as a very effective derivative, thereby preventing over-filling of the vascular apparatus and the formation of a congestive diathesis. That the menstruation may, however, occasionally present a *hemorrhagic* type in females with narrow and thin-walled vessels, was especially insisted upon in our consideration of chlorosis;[1] indeed, we are free to confess that, to our mind, these rarer menorrhagic cases of chlorosis in women appear to be in reality quite a complete analogue of the hæmophilia more commonly observed in males. We are, moreover, confirmed in this view by the fact that in male individuals the hæmophilia has sometimes been observed to disappear after the establishment of periodic hemorrhoidal bleedings (see p. 60).

In conclusion, we recur for a moment to another fact already alluded to several times, viz., that very commonly hæmophilia, besides presenting various intermediary fluctuations in intensity, undergoes a *gradual decline* in its average severity with *advan-*

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[1] See Vol. XVI. p. 522.

cing age; and that sometimes, after the spontaneous bleedings have recurred with less and less frequency, and the traumatic hemorrhages have gradually lost their bleeder character, the diathesis disappears apparently spontaneously in the later years of life. In searching for the natural causes of this frequently observed peculiarity in the course of the bleeder anomaly, the most obvious explanation, it seems to us, lies in connection with that *abatement in the physiological regenerative power in old persons*, which manifests itself, as is well known, chiefly in the sphere of *hæmatopoiesis*, and gives rise, among other conditions, to a marked tendency to *oligæmia* (see Vol. XVI., p. 303). It is certainly easy to see that just in proportion as the formation of blood takes place less actively, any *plethora ad vasa* that may have existed will be relieved, together with the tendency to hæmophilia bleedings, and that when this relief is incomplete, so that profuse hemorrhages still occur now and then, a much longer time will in general elapse after the attacks before the previous condition of plethora is reinstated. Hence, in old persons, as experience shows is actually the case, the spontaneous bleedings will probably occur only at longer intervals, and the traumatic hemorrhages will be of a less profuse character than in younger bleeders; indeed, the blood-mass may finally become so reduced in the former that the bleeder diathesis is kept latent for the rest of life.

The preceding views are intended to be regarded only as a provisional attempt to deduce from the empirical material obtained by autopsies and clinical observations a somewhat clearer conception of the *nature* and *pathogenesis* of hæmophilia. To be sure, our exposition, as we freely admit, still leaves unexplained many single points in the symptomatology and etiology of this remarkable affection, but we believe that justice has been done to at least some of the most important features of the disease in both these respects, so far as seemed possible to us at present without resorting to gratuitous assumptions.

Diagnosis.

It is often extremely desirable, especially with reference to a

prophylaxis of the bleedings, to be able to diagnosticate the existence of a congenital hemorrhagic diathesis *before* the unwelcome fact is forced upon our attention by the occurrence of a dangerous hemorrhage. Such a providential diagnosis, as we may term it, is, however, possible *only in hereditary cases* of the disease, or in those of *multiple congenital origin*, but *not* in the *primary and isolated* cases; because, although the manner in which the transmission and multiplication of hæmophilia usually occur is now fairly well understood, we are still ignorant as to the mode of its primordial genesis. It is evident, therefore, that in some cases, notwithstanding the most careful examination of the patient's history and family record, a diagnosis will be impossible until after the occurrence of repeated hemorrhages, while in other instances a failure to foresee the eventual outbreak should be regarded as almost a crime.

Far the most open to the suspicion of hæmophilia are, in the first place, all *individuals whose mothers belong to bleeder families*, whether these mothers are themselves bleeders—as is comparatively rarely the case—or, on the contrary, are entirely free from the disease (see p. 26). Still more certain becomes the provisional diagnosis, if other children in the family have already been subjects of the affection; and when this is the case, we shall at least err on the safe side if we continue to regard every male child born in such a family as a bleeder until future tests (accidental wounds, etc.) demonstrate the absence of a hemorrhagic diathesis (*quisquis illorum habeatur hæmophilus, donec probaverit contrarium!*). Indeed, when hæmophilia has once made its appearance in a family of children, the introduction of every new member, if a male, is always to be regarded with apprehension, even though no evidence of the disease is discoverable in the mother or her ancestry, for experience has shown that under such circumstances, where the disease has arisen *de novo* and has not been transmitted hereditarily, it far more commonly manifests itself in *several* children one after another than in a single one alone. On the other hand, *hæmophilia in the father* is a far more uncertain guide in the presumptive diagnosis of the disease in the child; while, if the father merely belong to a bleeder family without being himself a bleeder, the indication is

of very subordinate value. In fact, all experience shows that under the latter circumstances the chances are altogether in favor of the child's not being a bleeder. In the presumptive diagnosis of hæmophilia, therefore, the *cognatic* relationships of the individual afford indications of far more importance than the agnatic.

Still, as has already been mentioned in the Etiology, the general rule that the male offspring of mothers belonging to bleeder families are subjects of pronounced hæmophilia, is by no means without exception; indeed, many of these children, for reasons not well understood, remain entirely free from the affection throughout life, or at least the diathesis maintains a complete latency in them. The diagnosis, therefore, in male children related as above described, can never be more than conjectural, and can be fully determined only by the future course of the case. The absence of hemorrhages during the first few weeks of life, it should be remembered, is no indication of safety, for the disease frequently delays its appearance until the end of the first, or even into the second year. Should, however, the second year pass without the occurrence of hæmophilia bleedings, the chances will have diminished considerably, since, of the cases thus far carefully recorded, nearly 70 per cent. clearly manifested their nature before the expiration of this period (see p. 29). Still, even now the child is not entirely secure from a tardy outbreak of hæmophilia until the full growth of the body has been attained; from this time onward the immunity is complete, since there is *not a single* case on record of the outbreak of pronounced hæmophilia for the first time after the twenty-second year of life. This rule, however, applies only to the fully developed bleeder disease; the rudimentary forms may sometimes manifest themselves transitorily, for the first time, at even a later period.

Far different, on the other hand, is it with the presumptive diagnosis of hæmophilia in the *female* members of a bleeder family. In this sex the pronounced disease is so rare that its existence in a female, hitherto free from any of the symptoms, can in general be predicated only as a remote possibility, even though she belong to a bleeder family, and some of her nearest

male relatives (brothers, sons) be actual bleeders. Still, if the family have hitherto exhibited a marked tendency to the production of female bleeders; if, for instance, the mother and sisters be notorious bleeders, the possibility referred to becomes somewhat more definite, and in exceptional cases may even attain to a degree of probability. Even under these special conditions, however, our suspicions will frequently prove erroneous.

In marked contrast with the presumptive diagnosis of latent hæmophilia, that is, of the bleeder disposition, stands the *diagnosis of the manifest disease.* This, in pronounced cases, is usually unattended by the slightest difficulty, since the frequently recurring spontaneous bleedings, the extraordinary dangerousness of all traumatic hemorrhages from even the slightest causes, and the family history of the individual, together form an etiologico-clinical picture which is scarcely paralleled in distinctness by that of any other anomaly. As for confounding such fully developed cases of hæmophilia with other hemorrhagic affections, especially scurvy and morbus maculosus Werlhofii, the danger is comparatively slight, because these cases are most completely marked by that hereditary or congenital and habitual character which sharply distinguishes hæmophilia at once from all other varieties of the hemorrhagic diathesis. Nor is there any greater difficulty in recognizing well marked hæmophilia in the female sex than in the male; for when a female individual has once clearly manifested a congenital and habitual tendency to profuse and dangerous hemorrhages, there certainly need be no hesitation in characterizing the pathological condition as hæmophilia; least of all, if the patient belong to a family of bleeders.

Difficulties present themselves in the diagnosis of the manifest disease in the two sexes, as a rule, only when, 1. *The case in question is the first of the kind in the family circle*, and the hemorrhage is the *first* in the history of the patient; or, 2. When we have to deal with a *rudimentary* case, or with one running an *anomalous* course. In the first place, as regards the correct recognition of a *primary* case of hæmophilia, this is in general impossible during the first attack of hemorrhage, and we shall have to suspend our decision until repetitions of the bleedings

have determined the *habitual* character of the existing hemorrhagic diathesis. Still, in cases of this kind, hæmophilia may at least be strongly suspected if the individual present no other indications of disease, and be a *male child in the first or second year of life.* On the other hand, the presumption is *against* the existence of hæmophilia, when the primary manifestation of a hemorrhagic diathesis occurs in an adult without a hereditary history of the disease, and especially if the patient be a female. Finally, in *rudimentary* forms of hæmophilia, especially in those which present merely the clinical character of a *transitory* hemorrhagic diathesis, it will rarely be possible to recognize the affection as an imperfect development of a congenital bleeder disposition, except when *the case occurs within the limits of a bleeder family, and when other members of the same family circle present the disease in an unmistakable form* (see p. 23). Cases of transitory hemorrhagic diathesis, in which we have no such indications to guide us, will usually have to be excluded from the category of hæmophilia, and referred to some other dyscrasic affection of known nature, such as scurvy or morbus maculosus (see the two following articles).

Duration—Terminations—Prognosis.

The *duration* of hæmophilia as a congenital hemorrhagic disposition probably always corresponds, on the whole, with the lifetime of the individual, since even in those cases in which the affection fails to appear until after the first year, or gradually ceases with advancing age to manifest symptoms, the diathesis probably still exists in a latent form during the periods of apparent absence. When, however, the outbreak of the hæmophilia takes place at the very earliest period of life, and, as is unfortunately too commonly the case, the death of the individual results sooner or later from an attack of hemorrhage, then the congruence between the duration of the disease and the duration of life is clearly perceptible, and the habitual character of the affection stands out with special distinctness.

The above remarks as to the duration of the pronounced forms of hæmophilia will naturally apply also to those *rudimen-*

tary cases which are observed especially in the female members, but occasionally also in some of the males of bleeder families, since in these cases also the bleeder disposition must be regarded as congenital. As regards their *clinical* duration, that is, the period during which the hæmophilia bleedings manifest themselves, the rudimentary cases, as has been repeatedly pointed out, present a *double* type, since in *many* of them slight attacks of hemorrhage recur more or less frequently throughout life and therefore *habitually*, while in others the disposition remains entirely latent, with the exception of a single outbreak of greater or less intensity. The temporal course, therefore, of this latter type may present all possible varieties in the individual cases, and is in general bounded by no definite limits.

As regards, finally, the *duration of the hemorrhagic attacks themselves*, great differences are noticed also in this respect. In a case observed by Escherich, in Würzburg, the patient, a bleeder, bled to death in forty-four hours, from a slight cut received in a students' duel ; in another case, recorded by Wachsmuth, a young lady bleeder died during the wedding night, therefore within a few hours, from the effects of the defloration (rupture of the hymen); while in other cases hemorrhages have lasted several weeks before their termination in death, or their arrest just in time to save the life of the patient. That the attacks of syncope which take place towards the termination of excessive hemorrhages are not always the forerunner of death, but are rather in some instances the very means of saving life, has already been pointed out in our description of the symptomatology of the disease.

The *ultimate result* of hæmophilia in the great majority of cases is *death*, possibly in the very first attack, but usually from one of the hemorrhages in later life. The mortality of the disease is therefore very high, and at the same time also very premature, on account of the generally very early outbreak of the diathesis, and its intensity during the first period of life. A very large number of bleeders succumb to the murderous affection in early youth, the rate of mortality between the first and seventh years being particularly excessive ; while only a comparatively small proportion of bleeders suffering from the well-

marked and fully developed form of the disease escape the constantly threatening danger of a fatal hemorrhage, and at last reach the age when the diathesis is frequently observed to abate spontaneously or to become latent. There can be no question, therefore, as to the extremely pernicious character of hæmophilia, especially in childhood and youth.

Although the age is not definitely stated in all the hitherto observed fatal cases of hæmophilia, it is expressly mentioned in a very large number of the reports that the death occurred in "early childhood." Grandidier has compiled 212 cases in which the age at death was accurately known, and this table, which includes 197 males and only 15 females, shows clearly the excessive mortality of bleeder children between the first and seventh years of life:

	Males.	Females.	Total.
Within the first year	22	7	29
From 1 to 7 years	89	3	92
" 8 to 14 "	39	1	40
" 15 to 21 "	24	3	27
" 22 to 28 "	8	—	8
" 29 to 35 "	6	1	7
" 36 to 45 "	3	—	3
Over 50 "	6	—	6
Total	197	15	212

According to the above table, therefore, more than half of the entire number, 121 (111 males and 10 females), died from the affection before reaching the eighth year, and only 24 survived the twenty-second year. Instances are by no means wanting, however, in which bleeders have attained advanced age, even though the tendency to hemorrhages has continued undiminished. Thus, the head of the bleeder family Appleton-Brown died in old age (year of life not stated), of hæmaturia and bleedings from bed-sores (Hay); while Grandidier in his latest articles mentions patients—some of them perhaps still alive—who had passed their fiftieth, or even sixtieth year without having lost the tendency to hemorrhages.

On looking over the causes which have induced the fatal hemorrhage in individual cases, one cannot but be struck with the high mortality from trifling wounds. Thus, the record shows that the extraction of teeth, circumcision, and the application of leeches are specially dangerous; less hazardous, but still attended with danger, are the minor operations, such as venesection and cupping, while vaccination seems to involve but little

risk. Among the accidental wounds, those of the face (especially the lips) appear to be most apt to excite fatal bleeding.

The total number of known deaths thus far from extraction of teeth is thirteen, from ritual circumcision in Jewish children eight, and from the application of leeches five. Extremely dangerous, but not fatal hemorrhages after extraction of teeth, have been observed in more than forty cases. For further details, we are obliged by lack of space to refer the reader to the articles of Grandidier mentioned in the Bibliography.

In many cases of pronounced hæmophilia death results, even during the continuance of the disease, from other intercurrent morbid processes; still these instances bear but a small proportion to those in which the fatal result is due to fatal hemorrhage. Finally, as we have already pointed out repeatedly, the hemorrhagic tendency not infrequently decreases with the advance of age, or even becomes completely extinct, and therefore may be said to undergo an *amelioration*, or even a *cure*, in the clinical sense of the word. These favorable terminations of hæmophilia, to be sure, usually occur only after the individual has suffered from the marked affection during his entire childhood and maturer life, and therefore only in the period of physiological decadence; still, isolated cases are recorded in which the tendency to hemorrhages has ceased in youth, or even in childhood (Thore, Lemp, Heath, etc.). After the subsidence and disappearance of the bleedings, the health of the patient is, however, by no means always perfect; usually, either during the period of remission or after the disposition has become completely latent, the previously mentioned *complications* and *sequelæ* make their appearance, and delay or even absolutely prevent the full restoration of the patient's strength. Still, viewing the terminations of hæmophilia as a whole, an early death appears to be so much more frequent than the other observed results, that the fully developed affection must unhesitatingly be pronounced one of the most dangerous anomalies in the entire range of pathology. The rudimentary cases of hæmophilia are, of course, comparatively less dangerous; still, a fatal result is by no means unknown even in them. Thus, it occasionally happens that a hemorrhagic disposition, which has hitherto developed imperfectly, or has

even been completely latent, suddenly surprises one by its outburst in a profuse hemorrhage, which places the patient in imminent danger, or even actually destroys life (Zaar, Beyer, Otto, and others).

After what has been said, but little need be added in reference to the *general prognosis* of hæmophilia. When the affection has once clearly manifested itself with some degree of intensity in a child soon after birth or somewhat later in life, the prognosis must be regarded as, upon the whole, unfavorable, the chances being greatly in favor of a premature death ; while in the improbable case of a prolongation of life we must always take into account the extremely obstinate character of the anomaly. Should the child, however, survive the eighth year, some hope may now be entertained that the organism, by virtue of its increased power of resistance, will be able to withstand the future bleedings ; still the danger is by no means passed, for any one of the bleedings in later years may prove fatal. On the other hand, the prospect will naturally be much more favorable if a tendency to latency be indicated by the diminished severity of the bleedings, and especially if an actual latency be demonstrated by the fact that slight accidental wounds run their ordinarily favorable course. In the absence, however, of such satisfactory proof, one should be cautious about giving a more favorable opinion, because, even though the spontaneous bleedings have entirely ceased, the apparent recovery of the patient may at any moment be converted into a condition of extreme danger by some trifling accidental wound. Finally, if the affection even in advanced age shows no tendency to spontaneous involution, the general prognosis will continue to be very dubious so long as the disposition to profuse hemorrhages remains undiminished, and the latter occur from time to time with their former intensity.

When, on the other hand, we have to deal merely with a *rudimentary* form of hæmophilia, in which the disposition to hemorrhages is indeed *permanent*, but is only *slightly marked*, the general prognosis will naturally depend upon the average degree of intensity of the affection, and will therefore be, upon the whole, favorable *quoad vitam*. In such cases, moreover, a

complete retrogression of the diathesis in after-life, and therefore an actual recovery, can be calculated upon with much more certainty. In those anomalous cases, finally, in which the morbid disposition manifests itself only transitorily, the general prognosis coincides with the *special prognosis*, *i. e.*, with the *prognosis of the individual bleedings*, to which we now pass briefly in conclusion.

The *special prognosis of hæmophilia bleedings* is modified chiefly by the nature of the existing hemorrhage. External bleedings are, as a rule, more serious that the interstitial forms, and among the latter the subcutaneous hæmatomata involve much greater danger than the cutaneous hemorrhages (petechiæ, ecchymoses, vibices). · Next in importance comes the *situation* of the bleeding, since certain localities (the dental alveoli, lips, prepuce, etc.) are distinguished by specially profuse external hemorrhages. The locality is also of importance, in so far as it permits or interferes with the local application of styptics; hence, internal bleedings are, *ceteris paribus*, naturally more dangerous than the external. In the third place, when repeated attacks occur, the prognosis in any given hemorrhage will be largely modified by the severity of the previous attacks, and therefore by the *degree* of the existing diathesis. If the previous attacks have been extremely profuse and threatening, every succeeding hemorrhage will necessarily be regarded with increased apprehension. Still, if these large losses of blood have been well borne, so that the patient is known to have manifested a marked tolerance of diminutions in the volume of blood, this fact will, of course, enter as an important element into the present prognosis. The *age* and *constitution* of the patient are also important elements in cases of profuse and obstinate hemorrhage, because individuals of a very tender or very advanced age, or of a feeble constitution, will obviously be less able to withstand the exhaustion of such attacks. Finally, it should not be forgotten that the result in these hemorrhages, just as in other serious morbid processes, is often determined, not so much by the gravity of the local changes and the individuality of the patient, as by various external and purely accidental conditions; and these the physician, in forming his opinion as to the probable result,

should weigh with scarcely less care than he devotes to the more general conditions mentioned above.

Treatment.

Although hæmophilia is far from being a frequent affection, its great malignity, which has been the more clearly ascertained by reason of this very fact, renders the inquiry after a radical *prophylaxis* entirely superfluous.

So far, however, as a prophylaxis is possible, the end in view is two-fold: 1. To prevent the occurrence of *new* cases of the disease; and, 2. Where the bleeder disposition already *exists*, to check its manifestations (the hæmophilia *bleedings*). We may therefore speak of a *general* and of a *special* prophylaxis of hæmophilia.

As regards the *general* prophylaxis, the main fact to be dealt with is the marked transmissibility of the disease, since in by far the majority of cases pronounced hæmophilia is not of independent congenital origin, but is rather the result of direct, especially indirect, hereditary transmission (see Etiology). It is clear, therefore, that much might be accomplished in the way of checking, though not of entirely suppressing the further propagation of the disease, if, in spite of declamatory appeals for "the liberty of the subject" on the part of *doctrinaire* enthusiasts, *all marriages* likely to result in the procreation of new generations of bleeders were legally *prohibited.* In the absence of such a governmental restriction the physician is unquestionably warranted in using his personal influence to prevent such marriages, by pointing out to the individuals concerned the seriousness of the danger, and by appealing to their consciences to desist from a step which might involve disaster to their posterity. For, however little right the physician may have under ordinary circumstances to interfere in the private affairs of his patients, the evil to be avoided is here so great that energetic efforts to avert it are certainly in every respect justifiable. The same warning is equally necessary also in the case of healthy individuals, who, ignorantly or thoughtlessly, are on the point of connecting themselves by marriage with a bleeder family. Still, there is

clearly no warrant for such interference with the personal rights of individuals, whether by the government or by the physician in his private capacity, except when the danger is commensurate with the sacrifice required. To enforce celibacy, as W. Legg has recently advised, upon *all* members of bleeder families—males and females, bleeders and non-bleeders alike—merely because the disease may *possibly* appear in their offspring, seems to us to be carrying caution to excess; the most that we can reasonably demand is a restriction of this kind when there is a *probability* of the disease being transmitted. Now, as we have already seen, experience has shown that the capacity for transmission does *not* exist in *all* the members of the families, but only in certain categories of the same, and that in the other members the danger is so slight as not to require a prohibition of marriage. In this latter class may probably be included all *male* members of a bleeder family *who are not themselves bleeders*, since the transmission of hæmophilia by such individuals is among the rarest of clinical events. On the other hand, *marriage should be forbidden to all the females of a bleeder family without exception*, because the female sex possesses in an eminent degree the power of transmitting disease, especially hæmophilia, and this capacity exists in the non-bleeder as well as in the bleeder females of such families. In the case of a *male bleeder*, it is to be borne in mind that the children begotten by marriage with a healthy woman are, to be sure, frequently, but by no means uniformly, subjects of hæmophilia, and that while the danger of hereditary transmission is, therefore, greater than in the case of the non-bleeder males of such families, it is far less than that attending the marriage of the female members, either bleeders or non-bleeders. Still, generalizations of this kind are of little assistance when we are called upon to determine the risk in individual cases, and it will be far better, therefore, to be guided by the special history of the family as regards the mode in which the disease has hitherto been transmitted. Thus, if the record shows that repeated instances have occurred in which hæmophilia has been handed down in an agnatic direction (from father to son), the marriage would be morally unjustifiable; while, if the tendency to hereditary transmission has been noted only in the

female members, no reasonable objection can be urged against the marriage of a male member, even if he were a marked bleeder.

In this connection we may refer again to the two large bleeder families at Tenna, in Graubünden, in which families, according to Viele, the disease has always been propagated by the females and never by males, although the latter have all been marked bleeders, and many of them had numerous offspring by marriages with healthy women. Indeed, experience seems to have taught this community the natural solution of the question at issue, for we find that the marriage of the males in these families has come to be regarded as entirely unobjectionable, whereas in 1855 the few female members still living had all abstained from marriage. If the disease at Tenna do not desert the mode of transmission it has hitherto followed, there is good reason to expect its complete extinction in a not very distant future. We have not been able, however, at the present date (1875), to ascertain the number of bleeders still living in this part of Rhaetia, and are consequently not prepared to say how far this highly desirable result has as yet been actually attained.

In the preceding suggestions as to the general prophylaxis of hæmophilia are comprised the principles which, it seems to us, should guide the physician when he is consulted, or feels himself compelled to volunteer advice, in regard to a *contemplated* marriage where one of the parties belongs to a bleeder family. As we have seen, there are in these alliances favorable and unfavorable conjunctions, and the physician, who knows how to read aright the different constellations which are possible in such cases, will often be able to allay unnecessary anxiety or to avert an impending evil. The state of affairs is, however, of course materially changed when the marriage has already been consummated; the aspects must now be regarded as unfavorable, and the danger urgent that a progeny will result composed partly of actual bleeders and partly of conductors of the disease. The best that can be hoped for from such a marriage is that "nothing will come of it"—that it will remain unfruitful. The physician should, therefore, regard it as his duty, when opportunity presents, to emphatically express this ungracious wish to the married couple; but here his obligation naturally ends, and the task of prophylaxis must now be left to a private understanding between the individuals themselves.

The same remark will apply also to those cases in which a healthy married couple, *neither* of whom belongs to a bleeder

family, have, *from unknown causes*, begotten a bleeder child. Here, where the disease *has not been transmitted hereditarily*, but has evidently *arisen congenitally*, there is still reason to fear that the same prejudicial influences which have co-operated in the procreation and development of the first bleeder child, will continue to act in the future, since experience shows that in such cases the hæmophilia does not remain isolated, but reappears successively in several children. In this case also the danger of further progeny should be explained to the parents, and the future responsibily shifted to their own intelligent action in the matter.

Again, it may happen that a marriage which has resulted in the procreation of bleeder children may be dissolved by the *death of one of the parties*, and the question may then arise whether the *survivor* should be allowed to *remarry*. In deciding this question it will be necessary to ascertain definitely whether the affection in the children is of hereditary or of congenital origin. In the former case remarriage may be permitted, whatever the mode of transmission, whether through the mother or father, provided it can be shown that the deceased is the one through whom the conduction has taken place. For all experience hitherto has shown that in such remarriages no instance has occurred in which a man previously married to a woman of a bleeder family has begotten bleeder children by a second marriage with a healthy woman, or in which a healthy woman previously married to a male bleeder has contracted the latent disposition by such relation so as to beget bleeder children by a subsequent marriage with a healthy man. On the other hand, examples are not wanting in which the misfortune of begetting bleeder children, once begun by a wife from a bleeder family in her first marriage, has been continued in a second series of children by a subsequent husband (Grandidier, Reinert). Of course such a remarriage should not be allowed to take place without energetic protest.

When, however, the hæmophilia in the children is clearly *not* hereditary, but is of *independent origin*, it is naturally much more difficult to determine the relative degree of responsibility on the part of the two parents for its occurrence, and the question

of remarriage by the survivor is, therefore, to a certain extent an open one. Still, if we bear in mind the fact upon which we have already laid such repeated stress, that the capacity for transmitting hæmophilia inheres, in a far higher degree, in the female sex, the remarriage of the mother in such cases will appear much more objectionable than that of the father; and it will be seen to be altogether probable that, *even when the disease originates independently, it is mainly due to the influence of the mother*. What the real nature of these primordial influences may be through which hæmophilia is begotten in the fœtus we shall not attempt to decide; but we are satisfied that when bleeder children have appeared in a family, it is clearly advisable for the mother to abstain from remarriage, even though no cases of the disease had occurred on either side of her family previous to its appearance in her offspring.

The preceding remarks must suffice here to point out the way in which the state or the private physician may interfere to check the further propagation of hæmophilia, without unnecessarily sacrificing the rights of the individual; and if the directions given were strictly carried out, there is little doubt that in the course of time the affection would become considerably less frequent than it is at present. *A complete eradication of hæmophilia, however, by such means, is impracticable, and, in fact, impossible by any method known at present.* For until we have discovered those obscure *primordial causes* which every now and then determine the occurrence of *primary cases* of hæmophilia—after which the further propagation of the disease takes place in accordance with definite known rules—we shall never succeed in cutting away the deeper roots of the disease, and in thus eradicating it at the very start. The investigation of the primordial causes of the disease remains, therefore, now as in the past, the necessary preliminary to a radical prophylaxis; and the preventive measures suggested above, notwithstanding their great practical importance, will consequently always possess only a secondary value in the eradication of the disease.

In passing now from the general prophylaxis of hæmophilia—the prevention of new cases of the disease—to its *special*

prophylaxis, we come to a task of scarcely less importance, viz., the prevention of the *hæmophilia bleedings*. When the suspicion of such a diathesis rests upon a new-born child, all influences likely to excite these bleedings should, of course, be carefully avoided from its very birth, and especially after the existence of the affection has been demonstrated by one or more dangerous hemorrhages; nor should these precautions be withdrawn, either in the merely suspected or in the pronounced disease, until sufficient evidence has been accumulated by the results of accidental wounds, that involution has taken place, or that the original suspicion was incorrect. The special prophylaxis of hæmophilia, therefore, not only begins, when possible, with the birth of the individual, but in very many cases must continue even throughout life.

This vigilance, moreover, although of course necessary against *traumata* of all kinds, is to be directed especially against those likely to excite a *superficial* hemorrhage, because this form of bleeding has been found to be far the more dangerous to bleeders. Trifling injuries, particularly, should be sedulously avoided, because these are most apt to occur *accidentally*, and therefore require greater circumspection for their prevention. As regards the *intentional* infliction of wounds—even the most insignificant operations attended by loss of blood—the same precaution is equally necessary; even when indicated, they should not be performed if any other operation not involving hemorrhage can be substituted, or if the patient's condition does not demand the operation imperatively. When, however, surgical interference cannot be postponed, on account of the vital indications, the operator should prepare himself with all the means, to be presently described, for arresting the hemorrhage as speedily as possible.

To these general rules we may append a few special indications in reference to the prevention of wounds. First, as regards *accidental* injuries, care is evidently most necessary during the period from the birth of the child up to its eighth year, because the manifestations of the disease are most pronounced and the loss of blood most dangerous at this time, and because the patient is less competent to take the necessary pre-

cautions for himself. During school life, moreover, incessant watchfulness is still imperative, for now the child is exposed to danger from accidents in his boisterous play with his schoolfellows, as well as from his irrepressible desire for physical action of all kinds. If *gymnastic exercises* are a part of his school curriculum, however desirable they may be in other respects for his physical development, the family physician must see to it that the child is excused from engaging in them. Should this hard-fought battle of childhood be fortunately survived, there is still to be met the question as to his *future avocation* and his *physical responsibility* to the *state* and *community*. Of course, all the more directly *mechanical* employments, which involve any considerable danger of accidents, are unsuitable for bleeders; and, when a choice is possible, the child should be educated for one of the "learned" professions, in which he will be better protected from the rough contact of the external world. As regards *military service*, we agree entirely with Grossheim (l. c.), in his opinion that *all bleeders should be unconditionally exempt*, and the same remark will apply also to similar duties, such as the *fire service* required in many communities. These indications will suffice, without going into further details, to show the manifold character of the measures necessary in the prophylaxis of hæmophilia, and the serious importance of the disease in its social aspects.

As regards *operations*, little need be added to the general caution already given. There are, however, two operations—the one a religious, and the other a social duty—which are of such importance as to deserve consideration in some detail. We refer, of course, to the *Jewish rite of circumcision, and vaccination*. With respect to the former, while we have nothing to object to it in general as an honorable custom sanctioned by ancient tradition in a religious community of the highest respectability, we still agree with Henschel, Finger, and others, that its observance in Jewish bleeder families should be strictly prohibited in view of the unfortunate results that have attended the operation under these circumstances. The practice which has been adopted in certain Jewish families, of substituting baptism for circumcision, of course serves no moral purpose either for

Judaism or Christianity, and it seems desirable, therefore, that the rite should be modified in some way for Jewish bleeder children, so that they can fully satisfy the religious requirements of their faith without running the risk of hemorrhage.

As regards the now almost universal practice of *vaccination*, it is fortunate that this minor operation is attended with much less risk than circumcision, otherwise the mortality among bleeder children would inevitably have been far greater than it is. Indeed, experience has abundantly shown that vaccination is one of the *least dangerous* operations in bleeders, and there seems to be no good reason, therefore, why bleeder children should be deprived of its benefit. Still, the profuse hemorrhages which have occasionally occurred during its performance teach the necessity of the physician's being prepared with proper means for immediately arresting any considerable bleeding that may arise.

Among other minor operations, the object of which is simply curative rather than the fulfilment of a religious or social duty, may be mentioned, on account of their frequency, the *extraction of teeth*, *venesection*, and *cupping*. As regards the extraction of teeth, there are few points upon which writers are so unanimous as the extreme danger of this particular operation in bleeders. The patient, therefore, should be specially warned of this danger, and all the more because usually the family physician is not consulted, but rather some dentist who is not aware of the nature of the case; and because, moreover, the temptation to have the operation performed is particularly frequent in bleeders on account of their predisposition to violent rheumatic toothache. Less dangerous is venesection; still, this is never to be undertaken in a bleeder without urgent necessity—a condition which is not likely to occur frequently under the present indications for bloodletting. With respect to cupping, it is only necessary to remark that, while death has rarely resulted from its performance in bleeders, serious hemorrhages have not been uncommon. Indeed, all of these measures are contra-indicated, and should be replaced, when possible, by others which do not involve loss of blood.

Furthermore, every precaution should be taken to avoid all

influences which determine the occurrence of *plethora* and *congestions*. Under this head may be included everything which occasions for the time being any considerable distension of the blood-vessels, violent action of the heart, or a strong determination of the blood to the surface of the body: (1) the excessive use of fluids, particularly hot stimulating drinks (coffee, tea, alcoholic beverages); (2) over-indulgence at the table; (3) constipation; (4) severe bodily exercise, especially during warm, sultry weather, as well as at other times when the patient is laboring under vascular excitement; (5) intense mental emotion. On the other hand, the diet, while it should be moderate in quantity and easily digestible, ought to be of a nourishing character. In place of tea and coffee, cold milk may be used; and to quench thirst, water or lemonade in not too large quantities. Finally, the patient should lead a quiet, though not idle life, as free as possible from exhausting labor and mental excitement.

We have now given what appear to us to be the most important indications for the rational prophylaxis, both of the diathesis itself and of its manifestations—the hæmophilia bleedings; at the same time we have no hesitation in saying that at present more can be accomplished in the way of prevention than by attempts to eradicate the disease after it has once been established. At least none of the plans of treatment suggested thus far have stood the test of experience. To be sure, individual cases of partial or complete success, after the prolonged use of certain remedies, have been reported, but in other instances the same treatment has proved completely useless. When the bleeder disposition, therefore, already exists, we are practically limited to measures for the prevention of the bleedings, or for their arrest during the attacks of hemorrhage.

Among the various means by which it has been proposed to counteract the *hæmophilia disposition*, and thus to satisfy the *indicatio morbi*, may be mentioned, in the first place, the *tonics* and *astringents* employed with the view of strengthening the fragile capillaries. Thus, among the *tonics*, cod-liver oil has been advocated by Ricken, and *iron* by Heyfelder, Kopp, Martin, Vieli, and Legg. As regards the use of iron, Virchow has very properly pointed out the necessity of caution when there are evident indications of plethora or an excited action of the heart. These symptoms, however, are of such common occurrence in bleeders, either as habitual

manifestations of the disease or as forerunners of the bleedings, that the use of iron for prophylactic purposes must, upon the whole, be regarded as *contra-indicated.* Its temporary employment during the acute anæmia following profuse hemorrhages is, of course, not open to this objection; in fact, the advocates of this remedy in hæmophilia seem to have employed it especially at such times. *Astringents* have also been used in various forms: externally—tannin baths, ablutions with solutions of sulphate of iron, decoctions of sage, diluted vinegar, etc.; internally—preparations of bark, rhatany, cascarilla, and, during periods of vascular excitement, large doses of *acetate of lead*, *ergot*, and *ergotin*. Formerly, with the view of allaying the vascular excitement more effectually by diminishing the force of the heart's action, even periodical *bloodletting* was resorted to; but latterly, since this measure has been found to be so dangerous, *digitalis* in large doses, or *nauseants*, such as tartar emetic and ipecac, have been preferred, and in some cases the treatment by such depressants seems to have been followed by a temporary amelioration of the tendency to congestions (Grandidier). It is clear, however, that such remedies as the acetate of lead, ergot, digitalis, and nauseants, cannot be used for any considerable period, and that they are therefore adapted not so much to an extirpation of the diathesis as to a palliation of its manifestations at a time when they are seriously threatened. At such times, moreover, *saline cathartics*, especially Glauber's salt, have been used for the relief of the existing plethora. The latter salt was originally employed for this purpose as a domestic remedy in an American bleeder family, and is said not only to have exerted a favorable influence upon the course of the bleedings (*vide infra*), but also to have produced a permanent effect upon the diathesis itself. Still, this effect was by no means constant or lasting in all the cases; indeed, there is no reason to suppose that laxatives, any more than other drugs, can act in a directly curative manner upon the structural anomaly which underlies the disease.

In passing now to the *symptomatic therapeusis—the treatment of the bleedings themselves*—we are met at the outset by the question whether, in cases of *spontaneous external* hemorrhage of non-traumatic origin, the treatment for its arrest should be at once undertaken, or whether the loss of blood under these circumstances should not rather be regarded as exercising a beneficial derivative influence. For, since these bleedings are commonly preceded by various symptoms of plethora and congestion, and therefore probably result from engorgement of the vessels, it is certainly possible that in checking the hemorrhage prematurely we might do far more harm than good. This view has been expressed by numerous writers, both formerly and in recent times (Consbruch, Thormann, Lowthorps, Tamme Beth, Wachsmuth, Vieli, Stromeyer, and Legg): indeed, some of these

authorities maintain that, after a rapid arrest of the bleeding in such cases, severe and dangerous symptoms are observed, in the form of extremely violent palpitation, oppression for breath—in fact, even apoplectic attacks and general convulsions. Other writers, however (Reinert, Assmann), have not been able to satisfy themselves of any injurious results from the abortive treatment in spontaneous hemorrhages, and advise that energetic measures should be used at the very outset, just as in the traumatic bleedings. The question, therefore, is still a mootable one, and can only be decided by the results of future experience; still, our own conviction is that early interference in these cases is at times attended with danger.

Such delay, however, should never be continued *too long.* Its only object is the relief of the existing plethora, and when in the judgment of the physician this has been secured, he should at once interpose without waiting until the hard, full pulse and flushed appearance of the patient have given place to an anæmic condition of the vascular system, general pallor, and exhaustion. It is certainly far better in such cases to err on the safe side, for there can be no doubt that under any circumstances an excess of blood is to be preferred to a deficiency, and that it is no part of the treatment to permit the patient to pass into a state of pathological anæmia. Another contra-indication against long delay is the difficulty with which every protracted hemorrhage is arrested, on account of the altered (hypinotic) condition of the blood which ultimately results under these circumstances.

In the *traumatic external hemorrhages*, however, all authorities agree as to the necessity of *immediate* interference. Nor is there any difference of opinion as to the means by which the arrest of the hemorrhage is to be effected, the same remedies being equally suitable, whether the bleeding is of traumatic or non-traumatic origin, or whether the active treatment should be begun early or somewhat later in the attack. Of the means recommended for the arrest of these bleedings, some are *local*, others *general* in their action; a combination of both methods, however, will be found more effectual than a too exclusive reliance upon local styptics. Among the local measures, *compression*, continued for a considerable time, perhaps for days, is

the most reliable, and, when the situation of the hemorrhage permits, should be first tried, either by means of manual pressure or by means of a tampon, graduated compresses, cork plates, etc. Sometimes, however, in the smaller wounds, cauterization by nitrate of silver, or, in the larger wounds, the application of ice, perchloride of iron, or a solution of tannin, will suffice to produce a momentary coagulation of the escaping blood; still, to produce a permanent effect, such styptics should always be followed by compression of the wound. In using pressure, however, the danger of producing gangrene—an accident that has occasionally happened under these circumstances—should always be borne in mind, and the compression should not be more forcible nor longer continued than can be employed with safety (Grandidier). In the treatment of very small wounds, such as leech-bites or simple linear incisions, the twisted suture has in many instances been found of great service and but rarely followed by secondary hemorrhages. On the other hand, the actual cautery, and other applications producing a temporary crust over the bleeding surface, rarely suffice to arrest the bleeding permanently; they merely conceal the source of the hemorrhage for the time being, and only add to the difficulty of applying the compression which is generally afterwards required (Grandidier). Among the more frequent external bleedings, few present so much difficulty in their arrest as those which occur from the dental alveoli after the extraction of teeth. The most effectual treatment for this form of hemorrhage is the application of a tampon saturated with a solution of the perchloride of iron. The retention of the tampon may be effected either by a piece of cork—which is sufficient in some cases—or, still better, by the method recently suggested by Hohl,[1] viz., to cover the plug with a gold or silver plate clasped to an adjacent tooth by platinum wire, so as to effect permanent pressure for several weeks, if necessary. This operation can be readily performed by any dentist. At the same time other measures should never be neglected, such as the application of ice-bags, derivative foot-baths, and internal treatment so long as the hemorrhage continues. Great caution is necessary also in

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[1] Deutsche Klinik. 1871. Nr. 42.

regard to the too early removal of the tampon and its coverings.

As we have already mentioned incidentally, *internal treatment is always advisable* in these cases; indeed, it has not unfrequently happened that this method has succeeded in rapidly arresting the hemorrhage after local measures have proved entirely fruitless. In cases of internal bleeding, where it is difficult or impossible to use local styptics, we are of course compelled to rely exclusively upon internal remedies; but, even when the case permits the use of local treatment, the *combined* method by both *general* and local measures will be found to be more efficacious. Of internal remedies, the most trustworthy are *acetate of lead* and *ergot* in large doses frequently repeated (Schaefer, Wachsmuth, Meinel, Grandidier, et al.); the mineral acids, alum, tannin, and perchloride of iron, are less reliable for internal use. In every case, therefore, when the hemorrhage is at all serious, either acetate of lead in half-grain doses every two hours, or ergot in doses of 15 or 20 grains at the same intervals, should be given until the hemorrhage is arrested, or unmistakable symptoms of poisoning are produced. As regards the use of *Glauber's salt* in large cathartic doses, to control the bleedings of hæmophilia—a treatment recommended by Otto, who was struck with its success in the case of the bleeder family Smith-Shepard (see above), and was satisfied of its efficacy by trial in several of his own cases—the testimony in its favor is by no means uniform. Rieken and Elsaesser found it entirely useless; Wachsmuth, however, praises it highly, and insists upon its use at the very start in traumatic hemorrhages, and as early as the second day in spontaneous bleedings. He gives it in laxative doses of from three drachms to an ounce repeated daily. That the good effects, when obtained, result from the derivative action induced by the catharsis, is shown by the similar experience with other laxatives, such as *sulphate of magnesia* (Fordyce), *bitartrate of potassa*, *senna*, *tamarinds*, etc.

Furthermore, the directions previously given for the prevention of vascular excitement when a spontaneous hemorrhage is threatened, are obviously still more necessary when the bleeding, whether spontaneous or traumatic, has *actually taken place.*

Thus, it is extremely desirable during the hemorrhage that absolute rest and freedom from excitement should be strictly maintained. A low diet, and only a moderate allowance of cool drinks, with entire abstinence from alcoholic stimulants or hot liquids, such as tea or coffee, should also be enforced ; and, when circumstances permit, the bed should be placed in a large, airy chamber.

Of course it will not unfrequently happen, after these bleedings have continued for some time, that the *sedative* treatment above described will have to be replaced by the use of *restoratives.* Thus, when symptoms arise which threaten a complete arrest of the heart's action, such as a sense of suffocation, attacks of faintness, or actual syncope, the temptation to resort to *stimulants*—wine (champagne), brandy, rum, camphor, ammonia—for the purpose of supporting the patient through this crisis, is almost irresistible. Still, necessary as this mode of treatment undoubtedly is when the symptoms are extremely threatening, it is always to be borne in mind that syncope has sometimes proved to be the very means by which the hitherto uncontrollable hemorrhage has been arrested, and that, therefore, a too early resort to strong stimulants is undesirable. At all events, it is safe to say that stimulants are contra-indicated so long as there is reason to apprehend an aggravation of the hemorrhage from any considerable increase in the force of the heart's action. The same objection will apply also to the premature employment of *transfusion* (Grandidier), to say nothing of the danger of a *fresh* hemorrhage from the wound inflicted in the operation. To be sure, a few cases have been reported in which life has been saved at the last extremity by this means (Lane)[1]; still, except in desperate cases, it is far better, in our opinion, to avoid the operation altogether than to undertake it prematurely.

After the immediate danger from the hemorrhage itself has been passed, the profound exhaustion, which sometimes remains for days or weeks in the more serious attacks, is best combatted by efforts to *simply maintain life*, such as enforcing *the recumbent posture, and absolute rest of body and mind*, rather than

[1] The Lancet. 1840. p. 185.

by a direct resort to stimulants, restoratives, tonics, etc. For experience has amply shown that, *when the expenditure of vital force is restricted as far as possible*, life can often be maintained for a considerable period in man, just as in the lower orders of animals, upon very small supplies of food, air, etc., and that bleeders particularly possess a marked tenacity for life under these circumstances. In the administration of food, therefore, the quantity should at first be limited, and increased gradually as the appetite revives; while as regards liquids, the burning thirst from which these patients suffer (see Vol. XVI., p. 347) should be allayed by often repeated, but *small* draughts of cold water or cold milk, to which, so long as the pulse and heart-beat remain alarmingly feeble, a few drops of brandy or rum may be added. When the indication has been fulfilled, it is better to discontinue the use of such "restoratives," and trust simply to a gradual revival of the patient's strength by means of long-continued rest and a bland, easily digestible diet. By this simply hygienic and "unheroic" mode of treatment we shall at least most effectually guard against the premature occurrence of a new hemorrhage. For the same reason, caution is equally necessary in the use of all the more active tonics, and, therefore, the *ferruginous preparations* should be reserved for those cases in which the exhaustion and pallor continue for an unusually long time after the arrest of the hemorrhage. A trip to the country, sea-bathing, and other roborant measures may also be prescribed in such cases. On the other hand, when, as so often happens, the patient rapidly loses his pallor, and, like Uhde's patient (see p. 44), becomes again within a comparatively short time "as blooming as a rose," the physician may obviously content himself with enforcing the above restrictions as to rest and diet.

The *interstitial cutaneous hemorrhages* (petechiæ, ecchymoses, vibices) require no special treatment in bleeders, since the loss of blood is inconsiderable even when the extravasation into the tissue of the skin has been of large extent, and since, moreover, we possess no means for hastening the gradual involution which these *purpura*-efflorescences undergo *spontaneously*. As regards the treatment of the *subcutaneous* interstitial hemorrhages—the *hæmatomata*—it is of the first

importance to protect these tumors from mechanical injury, and to abstain from opening them prematurely by incision or puncture. The affected limb or part of the body is to be kept as quiet as possible, and an effort made to effect a gradual disintegration of the tumor by means of cautious pressure, the application of lead-water bandages, moist warmth (Priessnitz's compresses, poultices), etc. Opening should be resorted to only when the discolored appearance of the tumor makes it certain that gangrene has begun. In these cases, which are fortunately not frequent, caustics are preferable to the knife; still, even when the former are used, profuse and dangerous hemorrhages almost always ensue, requiring for their control the energetic employment of the various measures previously mentioned.

Finally, the *complications* of hæmophilia are to be treated in the same way as under other circumstances, with the important exception that all remedies should be carefully avoided which may possibly excite hemorrhage. Thus, in the *rheumatic affections*, which are so frequently observed in bleeders, local blood-letting and severe counter-irritants, such as blisters, the local application of tincture of iodine, and similar measures for the relief of pain, are contra-indicated on account of their repeatedly observed tendency in these cases to produce excoriations which give rise to uncontrollable bleedings. As substitutes for these stronger applications, therefore, we should prefer the milder rubefacients (spts. camphoræ, opodeldoc), or anodyne liniments containing hyoscyamus, chloroform, etc.; while the absorption of the effusion may be promoted by moist warmth, or by alcoholized watery solutions of iodide of potassium. It is important, moreover, that the painful and inflamed parts should be protected from mechanical injuries by soft coverings and supports. Furthermore, when the locality permits, bandaging the parts so as to secure absolute rest to the joints, muscles, etc., from both active and passive movements, will be found of great service just as in the ordinary forms of rheumatism. Lastly, some writers (Vieli, Grandidier) assert that in the treatment of these rheumatic affections the use of *mercurials* in any form, and however prudently administered, is commonly attended by a *temporary aggravation of the hemorrhagic diathesis*, and therefore should

be strictly avoided. We simply record this opinion without attempting to explain the supposed idiosyncrasy; but the warning, if well founded, will undoubtedly apply also to the treatment of the *other complications* of hæmophilia, particularly those of an *inflammatory* character. As regards these other complications, inasmuch as their usual course is not specially modified by their connection with hæmophilia, we have nothing further to add in the way of treatment, except to reiterate the fundamental caution already repeatedly given, viz., to strictly avoid all remedies or applications which in their effects involve even possibly the risk of hemorrhage.

Scurvy, Scorbutus.

(German: *Scharbock*.[1])

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[1] Writers differ as to the etymology of this word, the source of which is probably the same as that of our English "scurvy" and the Latinized "Scorbutus." Thus, some authors trace these terms to the Danish "Schorbeet, Schorbuck, Schoerbuch;" others to the Dutch "Scheurbuyk, Scheurbeck, Scorbeck" (ulcer of the mouth); others still to the old Saxon "Schorbock" (Reissen und Grimmen); and finally, others (particularly *Lind*) to the Slavonic "Scorb" (disease). The earliest mention thus far discovered of the German word "Scharbock" is to be found in the Botanologicon of *Euritius Cordus* (1534), where, in a passage on the remedial virtues of the lesser celandine (chelidonium minus), the writer says: "Saxones vero—(scilic. herbam dicunt)—*Scharbockskraut*, quod forte morbo, quem illi *Scharbock* nominant, medeatur.

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The preceding bibliography of scurvy is far from complete, and contains only the more important works on the subject. A more comprehensive enumeration may be found in Krebel's work (l. c.), which devotes a hundred pages to the bibliography of the disease, and gives a list of all the works which had appeared up to 1861, with brief accounts of their contents. This list includes the names of no less than 773 authors!

Historical Remarks.

In the following brief historical sketch it is not our purpose to present an extended résumé of this branch of our subject, but merely to point out those leading facts in the history of the disease which are important for a clear appreciation of its genesis.

Although neither the medical nor the historical literature of antiquity and the earlier middle ages contains a single passage that discriminates scurvy as a distinct species of disease, or even positively indicates its existence during these periods, it is hardly to be supposed that an affection so closely connected, as scurvy appears to be, with certain widely prevalent sanitary evils—particularly improper diet, hardships, and unfavorable

metereological influences—can have failed to manifest itself in all times whenever individuals or bodies of men have been subjected, under circumstances similar to those of recent times, to the influence of these noxious agents. So far, however, as *historical* evidence is concerned, the disease can be traced back only as far as the thirteenth century of the present era, and did not acquire actual historical importance as a frequent and widespread affection until about the middle of the fifteenth century, while its present name "scorbutus" made its appearance in medical and non-medical writings only at the beginning of the sixteenth century.

Attempts have not been wanting to prove the existence of scurvy in ancient times from certain descriptions of disease by the older writers, which have been supposed to refer to the affection in question. None of the evidence, however, will bear careful examination—much of it having no bearing whatever upon the point at issue, while the rest is at least untrustworthy. The most conspicuous instance of this misrepresentation is that which pretends to recognize scurvy in the affection described by Hippocrates, and after him by Aretaeus, Celsus, Caelius Aurelianus, Paulus Aegineta, Avicenna, and others, under the term "Σπλῆνες μεγάλαι (magni lienes);" still, as Hirsch has pointed out, there can be scarcely a doubt that these "enlarged spleens" are merely what is now known as the lesion of chronic malarial cachexia. The symptoms of scurvy were perhaps more closely simulated by those of a peculiar affection of the mouth called "Σκελοτύρβη," or "Στομακάκη," in which the gums became swollen, the teeth fell out, and a sort of paralytic weakness attacked the lower extremities. This disease is said by Strabo[1] to have prevailed in the army of Aelius Gallus, in Syria; Pliny,[2] moreover, mentions its occurrence among the soldiers of Germanicus in his Netherland campaign, and speaks of its being cured by the dietetic use of a fresh vegetable, the herba Brittanica (Rumex aquaticus, according to Muntingi). Still, on reading these accounts it is difficult to avoid the suspicion that the affection was not scurvy, but rather what is now known as diptheritic stomatitis. The same remark will apply also to the "oscedo" of Marcellus,[3] an oral affection, which has been supposed to be identical with the "Stomakake" of Pliny and Strabo, as well as with our modern scurvy, from the fact that Marcellus recommended for its treatment the herba Brittanica: "Oscedinem herba Brittanica viridis, sumpta in cibo lactucæ modo, sanat." The nearest approach to the symptoms of scurvy is unquestionably to be found in Hippocrates' description of the "volvulus sanguineus" (εἰλεὸς αἱματώδης), in his treatise on Internal Affections. The Latin translation is as follows:

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[1] Geograph. lib. XVI. c. f.

[2] Hist. natural. lib. XXV. c. 3.

[3] Lib. de medicam. c. 2.

"Morbus autem per auctumnum oriri incipit in eoque haec accidunt; ex ore malus odor exspirat, a dentibus gingivæ abscedunt et ex naribus sanguis effluit; interdum vero ex cruribus ulcera rumpunt et haec quidem vanescunt, alia vero exoriuntur; color niger est, cutis tenuis, ad deambulationem et exercitationem non promptus est . . . . hic morbus multa curatione indiget, alioqui non decedit, sed hominem ad mortem usque comitatur."

That the symptoms of this "volvulus sanguineus" strongly resemble those of scurvy cannot be denied; still, neither Hippocrates nor later writers give us any clue to the causes of the affection in question whereby the identity of the latter with scurvy can be satisfactorily established. Such an omission, moreover, when we bear in mind the marked, and indeed, characteristic etiology of scurvy, is fatal to the acceptance of supposed evidence of this kind from the ancient writers; and we can only conclude, therefore, that while the existence of scurvy in early times is *à priori* highly probable, direct proof of the suspected fact is still wanting. On the other hand, we possess unequivocal reports of the occurrence of scurvy at the time of the Crusades, in an epidemic form, and under external conditions completely similar to those ordinarily observed in more recent times, viz., want of food, hardship, unfavorable weather, etc., during marches and sieges. The first epidemic of this kind broke out in November, 1218, at the siege of the city of Damietta, among the forces of Count Saarbrücken, and continued through the entire winter with great destruction of life. Another epidemic, still more malignant, occurred in 1249, in the army of St. Louis, of France, when it was lying before Cairo and was suddenly deprived of its means of subsistence by an overflow of the Nile. The epidemic of 1218-1219 is described by Jacob de Vitry [1] as follows:

"Invasit praeterea multos de exercitu nova pestis, contra quam physici nullum remedium invenire poterant: dolor repentinus pedes invasit et crura, et conjunctim caro corrupta gingivas et dentes abduxit, masticandi potestatem auferrens; tibias horribilis nigredo offuscavit et sic longo tractu doloris afflicti cum patientia multa migraverunt ad Dominum plurimi; quidam usque ad vernale tempus durantes, beneficio caloris evaserunt liberati."

And Joinville [2] relates in regard to the plague of the year 1249:

"Et nous vint la maladie de l'Ost qui étoit telle, que la chair de nos jambes séchoit et étoit tardée de noir et de terre; et à nous qui avions maladie telle venoit chair pourrie aux gengives et nul n'échappoit. Le signe de la mort étoit, que là, oú le nez saignoit, it falloit mourir."

It is evident from these descriptions, in the thirteenth century, of what we can hardly fail to recognize as scurvy, that the disease had attracted the attention of historians long before it became the object of scientific investigation by physicians.

The immediate occasion of the increased nosological importance which scurvy suddenly acquired for the civilized populations of Europe in the second half of the fifteenth century, and

[1] *N. Krebel*, l. c. p. 8. [2] Histoire de St. Louis. Paris, 1761. p. 324.

continued to maintain for nearly three hundred years, was the wonderful transformation in the commerce of that epoch initiated by the bold voyages of the Spaniards and Portuguese, beginning with the discovery of America and of the passage to the East Indies. Whereas previous to this time the nautical enterprises of maritime nations had been almost wholly confined to coast voyages with frequent landings, and ship's crews, therefore, had only rarely been kept at sea for any considerable period, the spirit of adventure in the Old World now sought its scene of action upon the open seas, which thus became more and more the highway for purposes of conquest, colonization, and commerce. This extension of navigation, however, by necessitating the detention of the crews on shipboard for weeks or months at a time, naturally exposed them to certain sanitary evils, such as an impoverished and unvaried diet in connection with all kinds of hardships and deprivations. Under such conditions this affection, which from its comparative rarity hitherto had attracted but little attention, now became the great pestilence of ocean life, and, in fact, began its more important historic rôle among the nations of Europe as the special disease of *mariners*. So marked has been this peculiarity of scurvy up to quite recent times, that attempts have been made to distinguish, as regards the etiology and symptoms of the disease, between *sea* and *land* scurvy; but such a distinction can have no possible basis except in the general fact that the causes of the disease usually operate with greater intensity at sea than on land.

That this dreadful prevalence of scurvy at sea coincided with the beginning of modern navigation, and was in fact its most dangerous enemy, is shown very strikingly by the fearful epidemic of the disease which broke out among the crew of Vasco de Gama, in January, 1498, after the Cape of Good Hope had been passed on their way to the East Indies, and within a short time carried off 100 out of 160 of his companions.[1] In fact, the annals of seafaring nations are full of distressing accounts of the devastations occasioned by scurvy during the sixteenth, seventeenth, and eighteenth centuries, especially during the voyages to the

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[1] *Lind*, l. c. p. 349.

inhospitable Arctic and Antarctic regions. Thus, that admirable writer, J. Lind, in the preface to his classic work on Scurvy (1752), complains that "the scurvy alone, during the last war (ending in 1748), proved a more destructive enemy and cut off more valuable lives than the united efforts of the French and Spanish arms." The same writer also cites, from the history of maritime expeditions during the two centuries which had elapsed since Vasco de Gama's time, numerous instances in which the failure of important undertakings at sea had been wholly occasioned by outbreaks of this scourge.

Among the instances of this kind mentioned by Lind and others may be mentioned: the second voyage of J. Cartier to Newfoundland (1535), during which a large proportion of the crew died from scurvy; the expedition of de Monts, Pontrincourt and Pontgrave to Canada, towards the end of the sixteenth century; the circumnavigation of the globe by Lord Anson (1740–1744), during which the squadron lost 380 out of 510 men by scurvy; the expedition to the North Pole, under H. Ellis (1746–1747), and many other voyages.

The terrible devastations which scurvy had continued to produce at sea for several centuries at last awakened the governments more immediately concerned—particularly England—to the necessity of devising an effectual remedy. By the end of the last century the English government had been so far successful in controlling the disease in the navy and merchant marine by means of the enforcement of certain preventive measures, such as the better equipment and provisioning of all ships bound on long voyages, that scurvy has ever since been observed in the British service with constantly decreasing frequency, and is nowadays of comparatively rare occurrence. The example set by England was soon followed by other maritime states with equally gratifying results, so that this disease, which a hundred years ago was the spectre that inspired all mariners with terror, has never during the present century committed its former ravages at sea, except when entirely unforeseen events have occurred which exposed the ship's crew to certain deprivations (see Etiology). Indeed, it may happily be said that scurvy at sea, or, if one prefers the term much employed formerly—*sea scurvy*—is at present one of the rarest of morbid conditions, and

that the interest which attaches to this topological variety of disease is therefore mainly, though of course not entirely, merely historical.

Whereas the ships of the East India Company during their first voyages around the Cape were in the habit of losing nearly one-half of their crews from scurvy, the Company as early as the year 1775 was able to boast that, in consequence of improvements in hygiene, one of their vessels lost only a *single* man from this disease during the voyage (Black, N. Fontana [1]). Captain Cook, during his second three years' voyage to the Antarctic Ocean, lost only one sailor, who was already ill at the time of departure, while not a single fatal case occurred during O. v. Kotzebue's geographic expedition to the South Sea (1815–1818), or during the Arctic voyage of J. Ross in 1818. In the English marine the average loss from scurvy during the twenty years from 1850 to 1870 was only 0.15 per cent. of the total mortality (Friedel), and in the Austrian service, from 1863 to 1868, only 1.14 per cent. (Duchek),[2] while many other examples might also be cited in evidence that the disease on shipboard is far less frequent at the present day than formerly. Still, as these data equally show, sea scurvy is not yet completely eradicated, but still figures constantly on the disease-lists of marine boards; indeed, many recent experiences prove that the affection even nowadays breaks out with the same intensity as formerly when the usual precautions are neglected, or when circumstances prevent their being carried into effect. Thus, the crew of Captain Lasarew, during his voyage of discovery to Nowja-Semlja, were so severely attacked by scurvy that it was no longer possible to man the ship, and Lasarew was obliged to return; [3] while in Black's last expedition to the North Pole the *entire* company suffered from the disease.[4] For other examples, we refer the reader particularly to Krebel.[5]

While we possess authentic accounts of the occurrence of scurvy at sea as early as the second half of the fifteenth century, it is not until the first half of the sixteenth that reports begin to appear of the appearance of the disease on *land*. At least it is highly improbable that the singular affection mentioned by several historians as having prevailed in Saxony and Thuringia during the year 1486, and referred to subsequently by Fabricius in his "Annales urbis Misnicae" (1751) as an epidemic of scurvy, was really an outbreak of this character; in fact, all

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[1] See *Krebel*, l. c. S. 20 et 29.

[2] l. c. p. 277.

[3] Bulletin scient. de l'académie de St. Petersbourg. Vol. II. p. 139. 1837.

[4] Journal der neusten Land- und Seereisen. 8. H. S. 70. 1837.

[5] l. c. S. 28.

the symptoms point to its having been merely an epidemic of ergotism occasioned by the use of spurred rye (A. Hirsch). By the beginning of the sixteenth century, however, we find the disease prevailing quite extensively and with unmistakable symptoms along the coasts of Northern Germany, the Netherlands, Scandinavia, and the present Baltic provinces of Russia. References to this epidemic may be found in Euritius Cordus and Agricola (ll. cc.), and a more complete account in the later writings of Olaus Magnus, Echtius, Ronsseus, Wierus, Dodonaeus, and Brucaeus (ll. cc.) Even by this time the intimate connection of the disease with certain social evils, particularly famine, as well as with public calamities, such as wars and sieges, had attracted attention—Olaus Magnus, for instance, describing the affection as a "morbus castrensis, qui vexat obsesos et inclusos." In fact, somewhat more than a third of all the larger and more severe outbreaks of land scurvy which have been recorded for the period between 1556 and 1857 would come under this definition of Olaus Magnus, since 40 out of the 114 took place in besieged fortresses; and to this list may be added also the last important epidemic, which was observed in Paris during the siege of that city by German troops in 1871 (Delpech, Grenet, Dechambre, Hayem, Lasègue et Legroux, ll. cc.)

Among the more remarkable instances of this form of epidemic scurvy in former times may be mentioned: the epidemic at Breda during the siege by Spanish troops in 1625, when 1608 soldiers were attacked by the disease within the very short period of eight days; the epidemic in the Swedish army before Nuremberg in 1631, described by Roethenbeck and Horn; and the epidemic at Thorn (1703) during the Swedish siege, involving a loss of almost 6,000 of the besieged. Other accounts of a similar character may be found in the works of Krebel[1] and A. Hirsch.[2]

It is clear, therefore, that just as the outbreaks of scurvy at sea have occurred chiefly on the occasion of great nautical enterprises, so the disease has played its principal rôle on land as a war pestilence. The other epidemics of which we possess authentic reports may be divided into two classes: the *one* embracing the more severe outbreaks which were limited to con-

[1] l. c. S. 12 ff. [2] l. c. S. 534 ff.

fined localities, and the *other* those in which the disease prevailed epidemically throughout a considerable extent of country. The more severe *local* epidemics of scurvy during the last four centuries occurred chiefly in prisons, less frequently in barracks, hospitals, poor-houses, foundling asylums, etc.—in short, in buildings or groups of buildings the occupants of which have been subjected to overcrowding, uncleanliness, a lack of air and light, cold and moisture, and particularly an improper, unvaried diet. In consequence of the energetic efforts made in recent times to improve the general sanitary condition of such establishments, scurvy now occurs in them far less frequently than formerly, and even in prisons has been observed only in isolated instances during the last three decades. Thus, out of the 114 epidemics of scurvy, accounts of which have been compiled by A. Hirsch, 33 occurred in enclosed places of the kind mentioned above, and 12 of these in prisons; still, it should be observed that we do not possess reports of all the local epidemics which have actually taken place, and that, therefore, this branch of the statistics of the disease, as compiled up to the year 1857, can lay no claim to completeness.

Among the local epidemics of scurvy which have occurred during the present century may be mentioned particularly: the outbreaks of the disease in the Milbank penitentiary in London (1824), the foundling asylum at St. Petersburg (1831), the provincial jail at Prague (1836), the prisons of Christiania (1844), Alexandria (1844), and Pesth (1846), the Salpêtrière at Paris (1847), the workhouse at Constantinople (1848), the barracks of the Austrian troops at Rastatt, as well as the Strassburg prisons (all of them in 1854), the insane asylum at Aix (1853–56), and the prisons and workhouse at Ronnes (1856). To this class of epidemics belongs also the outbreak of scurvy among the French prisoners confined in the casemates at Ingolstadt (1871), among whom, however, only 159 were attacked out of a total number of 10,000 (L. Doering).

After deducting from Hirsch's list of the land epidemics of scurvy those which occurred in besieged fortresses and other inclosed situations, there remain, finally, forty-three instances of the *pandemic* occurrence of the disease. That this number represents with a fair degree of accuracy all the more important instances of this kind for the past three centuries, may be safely inferred from the attention which the historians of this period

seem to have devoted to the description of epidemics in general; and we may reasonably conclude, therefore, with Hirsch, that while the disease was formerly more frequent and widespread than now, *it by no means possessed that universal importance in the past which has been ascribed to it by many writers.*

This view, we are aware, is absolutely opposed to the opinion held by many of the older as well as more recent observers, that scurvy was really the dominating affection of the seventeenth and eighteenth centuries, and that during this period the entire population of Europe, not to say the whole world, was laboring under a "constitutio sæcularis scorbutica," resulting from certain unknown atmospheric and telluric conditions. The introduction of this conception of a permanent scorbutic constitution of disease operating during this entire period has led to so much confusion in modern medical literature, that it may not be out of place here to explain briefly the way in which the error arose. The whole responsibility for this confusion must be ascribed to the influence of the writings of Severinus Eugalenus, whose work on scurvy, published in 1604, and since then frequently quoted as an authority, has done much to spread false views of the clinical nature of the disease. In place of the clear, though necessarily incomplete descriptions given by his predecessors, Eugalenus substitutes a picture of the disease drawn with such hazy outlines that it might include pretty much the entire special pathology of the present day, and did, in fact, embrace all of it with which he was himself acquainted. Indeed, on reading his work, one is actually at a loss to decide which is the more amazing—the colossal self-complacency with which he distorts facts, or the complete lack of connected thought and natural powers of observation displayed in almost every sentence.

The first four paragraphs, which are devoted to the causes and the actual symptoms of scurvy, have been shown by Lind to be incomplete extracts taken at random from Wierus, and this portion of the work, it is scarcely necessary to say, contains everything of value to be found in the entire bulky volume. The rest of the dogmatic part (forty-five paragraphs) was wholly the intellectual property of Eugalenus, and consisted of a long medley of descriptions of other morbid conditions and symptoms (particularly those pertaining to the secretion of urine), which had nothing whatever to do with scurvy in either the past or the present acceptation of

this word, but which he proclaimed with much emphasis as the chief signs of a *constitutio scorbutica*. The work concludes with a series of "observations," in regard to which it is sufficient to say that the greater part of them were not cases of scurvy at all, although he reports them as such with the greatest assurance.

We should certainly not have delayed so long upon this work of Eugalenus, had it not played a very important part in the history of the literature of scurvy, and been regarded for nearly a hundred years as the "canon scorbuticum," so that even intelligent investigators were scarcely able to emancipate themselves from its influence. Indeed, most of the writers who treated the subject during this period were merely the blind followers of the teachings of Eugalenus, and even surpassed him at times in their extravagant assertions. Thus, Sennert declared scurvy to be the most multiform of all diseases; Drawitz held that all children were scorbutic from the moment of conception; while in the opinion of Moellenbroeck all diseases were complicated by scurvy, or, according to Bontekoe, were directly produced by it. From these expressions we may judge how rank a growth of weeds sprang from the seeds sown by Eugalenus; in fact, we have here only another illustration of what the experience of all times has demonstrated, viz., that no doctrine, however absurd, will lack adherents, provided only its prophets display the necessary audacity. Indeed, the disciples in such cases, as we have seen here, are usually not content with a blind faith, but must needs outdo in recklessness even the master himself.

In the course of time, however, a reaction naturally took place, and although a few shrewd observers like Sydenham, Fr. Hoffmann, Mead, Kramer, and Willis, contented themselves with protesting more or less forcibly against these extravagant delusions, without absolutely denying the existence of such a disease as scurvy, others went to the opposite and equally false extreme of proclaiming its non-existence and forthwith striking it out of the list of recognized affections. While this conflict of opinion, which began during the first half of the eighteenth century, was still raging fiercely, there appeared in 1752 an admirable monograph on the disease, by J. Lind, which by its quiet, philosophical tone, did much to allay the strife, and entitles him

unquestionably to a superiority over all other writers on this subject, whether ancient or modern. With a rare skill, which might serve as a model for all time, he not only separated the wheat from the heaps of chaff accumulated by his immediate predecessors, and restored in its true outlines the picture of the disease drawn by Olaus Magnus, Echtius, Wierus, and other older writers, but he also retouched it with such fidelity to nature by numerous observations of his own, that little is left to later observers except to copy him as the master.

Now, as Hirsch well says, the simple fact that such a complete chaos of professional opinion upon the subject of scurvy continued to exist for more than a century before the time of Lind—one party imagining that they could detect the secret influence of the disease in every morbid condition they encountered, while their opponents obstinately refused to acknowledge the existence of scurvy at all—this fact affords in itself a fair presumption that the majority of medical writers on the subject during this period had no opportunity of observing for themselves any considerable number of consecutive cases of the genuine affection. If this inference be correct, it is clear that the prevalence of scurvy, even at the time of its supposed general sway, was far from being so universal and permanent as many later writers imagined, and that such epidemics as did occur are not to be viewed as clinical manifestations of a mysterious secular anomaly of the human constitution, but rather as the result of definite injurious influences which were limited to certain times and places.

At the same time it is entirely compatible with this conclusion to acknowledge that during the seventeenth and eighteenth centuries scurvy was a far more frequent and widespread affection, not only at sea, as was proved above, but also on land, than it has been during the present century. For, even admitting, as we must, that the historians and medical writers of those times frequently mistook petechial typhus, or even epidemic ergotism, for outbreaks of scurvy, it would certainly be carrying our skepticism too far to maintain that the present rarity of the disease on land is proof of its equal infrequency in the past. On the contrary, it can hardly be doubted that the same special conditions

which excite local epidemics of scurvy in our own day—as in the late Franco-German war—must have operated with far greater intensity at a time when the present sanitary regulations were unknown, and that it is entirely to these hygienic improvements we owe our present comparative freedom from this popular scourge (Krebel, Hirsch, Duchek, and others). Indeed, the success which has already attended the adoption of such measures, especially within the last thirty years, fully justifies the hope that, as our knowledge of hygiene advances, epidemics of this kind on land as well as on sea may in time be reduced to a minimum.

In view of the few opportunities for observing the disease on any large scale during the present century, it is not surprising that but a comparatively small number of comprehensive monographs have appeared within this period. Among the more recent works which deserve particular attention since the time of Lind, may be mentioned those of G. and W. Samson von Himmelstiern (1843, 1844), Cejka (1844), Fauvel (1847), and Lilienfeld (1851); furthermore, the works just referred to, by A. Hirsch (1860), Opitz (1861), Krebel (1862), and Duchek (1861, 1870); and finally, the in part excellent contributions of French writers on the epidemic at Paris in 1871 (see conclusion of the Bibliography).

A few words, finally, in regard to the *geographic* distribution of scurvy during the period within which the affection has been distinguished as a special form of disease. Just as the affection has occurred at sea under all latitudes—high and low—but with especial frequency and violence on expeditions to the Arctic and Antarctic regions, so on land it has prevailed epidemically both in cold and hot climates, but particularly in the northern territories of the eastern hemisphere. Thus, out of the 114 epidemics of land scurvy compiled by Hirsch (see above), 31 occurred in *European* and *Asiatic Russia*—a far larger number than occurred in any other country of the eastern hemisphere. In fact, the last great epidemic took place in Russia in 1849, during which year 260,444 individuals, living in 16 different departments of the kingdom, were attacked by the disease, with a mortality of 60,958.[1] Widespread epidemics have also often been

[1] *Krebel*, l. c. S. 19.

observed, though with less frequency, in *Germany* (12 times), the *Netherlands*, *Norway* (particularly in Finmark), *Denmark* (in Copenhagen, the last time in 1846 and 1847), and in *Iceland* in connection with the famine of 1836 and 1837. In the *British Islands*, on the other hand, and in *France*, *Spain*, *Italy*, and the Balkan peninsula, the disease has been less prevalent, notwithstanding the statements to the contrary by the superficial writers of the school of Eugalenus. In regard to the land epidemics which have occurred in non-European countries, our information is incomplete, except perhaps with reference to the outbreaks in Asiatic Russia; still, we know that in the East Indies the disease has prevailed epidemically at numerous times during the present century, and with special violence in 1833 and 1840 (see A. Hirsch).[1] During the last few decades numerous aggravated cases of the disease occurred also among the horde of adventurers who flocked to the gold diggings of *California*, and were there exposed to the most distressing privations (Logan). In Australia, also, scurvy is said to have been observed very frequently of late, especially among the travellers on the expeditions to the interior of the country (Beckler). It must be sufficiently clear from these few details as to the geography of the disease, that although the affection prevails with greater frequency in some regions than in others, it possesses on the whole a thoroughly international character, and is by no means restricted to particular localities; and that, furthermore, the essential causes of scurvy are in no way connected with any definite modifications of climate, because every variety of these conditions is met with in the countries and zones where severe outbreaks have been of common occurrence (see also the Etiology of the disease).

General Definition of the Disease.

Scurvy may be defined as a *constitutional disease*, traceable in most cases to a definite *violation of hygienic laws*, particularly to *defective and improper alimentation;* generally characterized.

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1 c. S. 540.

moreover, by an insidious access, a lingering course, and a variable mode of termination, and manifesting itself clinically by an intense *general cachexia* in connection with various local eruptions and disorders of a hemorrhagic and hemorrhagico-inflammatory character. That the affection belongs properly among the *general disorders of nutrition* is apparent both from the profound constitutional disturbance, which precedes for a shorter or longer period the outbreak of the local symptoms, as well as from the fact that these manifestations affect the most different organs and regions of the body (skin, mucous and serous membranes, muscles); still the special pathological character of the tissue-changes in scurvy clearly entitles it also to a position among the *hemorrhagic forms of disease*, while its resemblance in certain particulars to the congenital and habitual hemorrhagic diathesis, or hæmophilia, treated of in the preceding article, would seem to render the present arrangement peculiarly appropriate. Not that there is any practical difficulty, as was repeatedly observed in our consideration of hæmophilia, in distinguishing between the two diseases, for they differ not only in many of their symptoms, but even more radically also in their etiology—hæmophilia being a congenital or hereditary and more or less permanent affection, while scurvy, on the other hand, is an *acquired* constitutional anomaly induced by *external causes*, and in favorable cases presents a distinctly *transitory* character. Still, the present order of treatment has the obvious advantage of accentuating both the contrasts and the resemblances between the two diseases far more sharply than would be possible by a more disconnected arrangement.

Etiology.

That *individuals differ in the predisposition* to scurvy, just as to most other morbid processes, is quite apparent from the common experience during epidemic and endemic outbreaks of the disease, that, out of the entire number of individuals exposed, only a portion are attacked, while the rest escape entirely; but to what personal conditions this special susceptibility or immunity is due, it is impossible at present to state precisely. At all

events, it is clear that such factors as sex, age, and constitution, although perhaps not entirely without influence, are of merely subordinate importance so far as the *relative* frequency of the disease is concerned, since under the same external conditions scurvy has been noticed to occur in women as well as in men, in the young as well as in the old, and in feeble as well as in hitherto robust individuals.

Of course, in all the statistics which give merely the *absolute* frequency of scurvy, these distinctions of sex, age, and constitution are very noticeable; but a simple glance at the circumstances under which such differences in morbility have occurred will show that they were dependent not so much upon inequalities in the internal disposition as upon purely *external* causes. Thus, the far greater frequency of scurvy in the male sex may readily be explained by the fact that men have been much more exposed than women to all those influences at sea as well as on land, which experience has demonstrated to be most likely to produce the disease (see Historical Sketch). So also the greater prevalence of scurvy, not only among males, but also among those in adult and middle life, as well as of a previously vigorous constitution—although we have no exact statistics on this point—is doubtless owing to the circumstance that these qualifications are commonly requisite in those selected for maritime or military service. If we leave out of the question, however, these purely incidental circumstances, which have of course largely determined the absolute frequency of scurvy, and confine ourselves to those statistics which bear directly upon its relative frequency, we fail to find any such important and constant differences, at least as to *sex* and *age*, as would warrant the conclusion that either of these conditions materially modifies the natural disposition to the disease.

To be sure, epidemics of scurvy have occurred in which more women were attacked than men, as in the epidemic of 1803 in South-eastern Hungary, recorded by F. v. Schraud, and one in Croatia in 1707, of which Ozanam reports that women only were affected; still, the fallacy of inferring from these facts that women possess a stronger predisposition to the disease than men is shown by the circumstance that in other epidemics, occurring in the midst of a mixed population, many more men were attacked than women (Legroux and others). That

scurvy, furthermore, although far more frequently observed in adults and mature life, attacks also children and persons of advanced age, is shown by the epidemic outbreaks of the disease in foundling hospitals (epidemic at St. Petersburg in 1831, reported by Doepp) and among the aged occupants of asylums and charitable institutions (Chrastina). An interesting fact in this connection is mentioned by Fauvel (l. c.), though, as a single instance, it cannot be regarded as evidence of a general predisposing importance of age, viz., that during the severe epidemic in the Salpêtrière at Paris (1847) the disease occurred only in *old* women.

On the other hand, the *constitution* seems to exert a somewhat more definite influence upon the susceptibility to the disease; at least, it has been a common experience both in sea and land epidemics that persons in *feeble* health are attacked earlier, in larger numbers, and more severely than the robust, although the latter, as we have already seen, possess no immunity against the disease. So, also, persons who are already *suffering from other diseases*, or *from the effects of some recent attack of disease*, seem to be specially sensitive to the influence of those determining causes under which scurvy generally occurs (see later). Thus, persons who are suffering from *intermittent fever*, *dysentery*, or *syphilis*, or have recently had an *attack of hemorrhage*, or been *wounded*, are said to be attacked by the disease with unusual readiness (Duchek, Krebel, and others).

The evidence of such a predisposing influence is most satisfactory in the case of *malarial disease*, either existing at the time or recently recovered from. Duchek states that of nineteen scurvy patients examined by him, fourteen came from malarial districts, and that in all of these the enlarged spleen of intermittent fever was distinctly noticeable; furthermore, in his hospital service at Lemberg scurvy figured at 1.5 per cent., and intermittent fever at 33.6 per cent. So also Wolfram [1] mentions the statement of Krischker, that, during the epidemic of scurvy at Rastatt (1852), intermittent fever was generally prevalent, and that in fifty-one cases the intermittent fever was complicated with scurvy, while in sixty-seven cases of scurvy attacks of intermittent fever supervened during the course of the disease. With respect to the combination of *dysentery*, *syphilis*, *hemorrhages* and *wounds* with scurvy, see particularly the reports of Krebel,[2] especially his observation in regard to syphilis, that venereal patients who have several times undergone mercurial treatment manifest an exceptionally strong disposition to scurvy

Unquestionably, however, the development of scurvy depends far less upon predisposing pathological factors than upon the

[1] l. c. S. 157. [2] l. c. S. 177 ff.

determining causes, since countless cases are on record in which individuals in the full enjoyment of vigorous health were stricken by the disease as a direct result of exposure to certain external influences. The general nature of these external influences has been fairly well determined; but whether the same influences are at work in *all* cases, in the sense that there is a *uniform* etiology of scurvy, is not in our judgment definitely settled by the present evidence. At all events, we agree with Duchek and others, that the mere fact of scurvy having occurred in numerous individuals and widespread epidemics notoriously under the operation of *one and the same* noxious influence, is in itself no evidence that the clinical complex of symptoms may not occasionally, or even frequently, be developed in *quite a different manner*.

That clinical processes of the same nature may, under certain circumstances, be excited by the most dissimilar causes, is taught in nearly every chapter of special pathology where the etiology has not been adopted as the basis of classification; and we should hardly have thought it necessary to dwell upon the point here, had not so many distinguished observers, particularly A. Hirsch, strongly insisted upon an uniform etiology for this affection.

The observation that scurvy occurred far more rarely as an isolated affection than in the form of local or extensive epidemics naturally gave rise, in the course of time, to the inquiry whether scurvy might not in reality be a *specific infective disease* of a *contagious* or *miasmatic* nature, like syphilis or malarial disease. In fact, not only the miasmatic, but even also the *contagious* nature of scurvy, has been maintained by many of the older writers (Echtius, Horst, Cameau, Poupart, Brambilla, and others), and recently also by Rottwil.[1] There are, however, important objections to classing scurvy among the contagious processes, particularly the circumstance that the disease has never been observed to be conveyed from one place to another, either by scorbutic patients themselves, or by fomites or other objects with which the patients have come into direct contact (Lind, Schraut, Larrey, and others). The conception, therefore, that scurvy is transferrable by means of a true contagium, that

[1] Nassauische med. Jahrbücher. Bd. XVI. S. 749.

is to say, a specific virus reproduced in the bodies of persons affected by the disease, must obviously be discarded, and all the more since the facts adduced in proof of this theory are susceptible of a different interpretation.

The fact upon which the contagionists mainly rely is the occasional occurrence of the disease in infants, who have been nourished exclusively by the milk of their scorbutic mothers (Rottwil, l. c.). In these cases it is supposed that the mother's milk contains the specific contagious matter, and acts as the vehicle of infection. This evidence is, however, obviously unsatisfactory, even if we admit, as we are disposed to do, that the scurvy in the infant was actually induced by the milk of the scorbutic mother, and not by other external causes. Certainly it is much more reasonable to suppose that the mother's milk in such cases, being secreted by a diseased body, is less nutritious than healthy milk, and produces scurvy in the child, not by reason of any positively poisonous and contagious properties, but simply in consequence of its being an *improper* and *defective* food.

On the other hand, it is much more difficult to disprove the possibility of a *miasmatic* origin of scurvy in *numerous* individual cases and local epidemics. Thus, the occasional occurrence of scorbutic affections in persons whose diet has not been defective in any of the particulars to be presently described, but who have lived in unhealthy apartments and been obliged to breathe impure air or drink water of a suspicious quality, would naturally lead one at first sight to concede the possibility of infection by means of a specific miasm introduced through the air or drinking-water. Still, such a view of the genesis of scurvy can of course apply only to a very limited number of cases, and as a general explanation is obviously untenable ; for no fact in the etiology of scurvy has been more clearly demonstrated by repeated and exact observation than the direct connection of the vast majority of isolated and epidemic occurrences of the disease with certain anomalies of alimentation, and for these cases, therefore, an additional factor, such as this hypothetical miasm, would be manifestly superfluous. Nor is the hypothesis in question at all necessary for even those exceptional cases which do not conform to the usual etiology of the disease. Certainly, until some positive evidence is adduced of the existence of such a miasm, it is far more reasonable to assume a non-infective origin for these, equally with the ordinary forms of scurvy, and to suppose that

in exceptional instances impure air or drinking-water and other sanitary faults of a general nature may not only predispose to, but even directly induce scurvy, just as we see the disease more frequently occasioned by an improper diet without the aid of miasm. With these remarks, therefore, we dismiss the miasmatic theory as unproved either in its general or limited application.

To pass now to a fuller consideration of those anti-hygienic agencies to which we have already repeatedly alluded as the most commonly observed conditions of scurvy, we find that the most important factor in the genesis of the disease is unquestionably a *defective dietary.* Although this general fact has long been recognized, opinions have differed widely, and still differ, as to the *particular dietetic error* which is the actual cause in the majority of scorbutic affections. Some have supposed that it consists in *a mere deficiency of food;* others in the use of *decomposed food* and *bad drinking-water;* others still in the *excessive use of certain articles of food*, particularly *salt meat* and *salted provisions;* and finally, others in the *absence of certain alimentary substances*, such as *fresh vegetables* and *fresh meat.* Still, as Duchek pertinently remarks, although all of these hypotheses are supported by ample real or apparent evidence in the history of scurvy, none of them is by itself capable of explaining *all* cases of the disease.

The theory which ascribes scurvy to a *simple deficiency of food* is based by its supporters (Milman, van Swieten, Canstatt, and others) upon the frequency of epidemics during famines occasioned by a failure of the crops, wars, and other public calamities, and upon the fact that at such times the disease selects the poorer and more badly-fed portion of the population. Hirsch, however, has shown that scurvy has by no means been a constant accompaniment of the so-called famine years, and numerous instances are on record in which the disease has raged with great violence under circumstances when the supply of food was ample as regards *quantity* and defective only in its *quality.* Still, although it is highly probable that the only connection between starvation, or a general deprivation of food, and scurvy lies in the simultaneous exclusion of *particular* articles of food, it is difficult to reconcile this conclusion with the fre-

quently observed absence of scurvy in other cases of famine. Was the diet in these cases merely deficient in such substances as might be withdrawn without incurring the risk of scurvy, or were other conditions present which counteracted the influence of the impoverished nourishment? Unfortunately, we have no means at present for answering these important questions definitely.

As a concomitant of famine, scurvy has been noticed particularly in Sweden (1784); in St. Petersburg, Cronstadt, and other places in Russia (1785); in Braila, when the country was occupied by Russian troops during a failure of the crops (1787 and 1793); in Hungary (1803); in Southern Russia, in consequence of the ravages of locusts (1823); in Iceland (1836 and 1837); in Prague, after the failure of the potato crop (1843); in England, Scotland, and Ireland (1846–47); in Russia (1847–49), etc.[1] On the other hand, scurvy has been repeatedly observed in various public institutions at times when the supply of food was ample in quantity; thus, in the prison at Clairvaux (1840); in the Salpêtrière (1847); in a poor-house at Constantinople (1848); in the deaf and dumb asylum at Breslau (1854); in the asylum on the Alser in Vienna, etc. (A. Hirsch). On shipboard, also, outbreaks of scurvy have occurred even when the crews were well supplied with food as regards quantity, although, of course, the affection more commonly makes its appearance when the supply of provisions has begun to fail and it has become necessary to diminish the daily allowance.

Since a mere deficiency of food, therefore, seems to be of only secondary importance in the development of scurvy, it remains to inquire somewhat more closely into the etiological relations of the *quality of the food*. In numerous instances scurvy has been noticed to occur both at sea and on land in connection with the prolonged use of *spoiled food*, such as mouldy ship biscuits and semi-putrid meat. Although in the majority of these cases the patients were driven to the use of such articles by the lack of any better food, still, instances are not wanting in which the disease appeared to be developed simply because spoiled food had been unnecessarily added to an otherwise sufficient diet, or because the individuals who were amply supplied with other food had resorted to the use of such substances in consequence of a perversion of appetite.

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[1] See A. Hirsch, l. c. S. 550.

Thus, Coale reports that on the frigate Columbia, during her voyage around the world with a crew of 480 men, diarrhœa and afterwards scurvy broke out, notwithstanding the abundance of good provisions in general, as soon as the supply of meat and biscuit taken on board at Bombay was found to have become spoiled. Similarly the ravages of scurvy among the gold-diggers of California have been ascribed chiefly to the use of semi-putrid meat (Logan); although in this case the result was doubtless due in part also to the lack of food in general, and to the extremely unfavorable external conditions to which these persons were subjected. Of special interest in this connection is the case reported by Molitor, of a healthy soldier twenty-eight years of age, who suddenly acquired a passion for eating raw putrid meat, and after a time became scorbutic and died. These examples, to which others might easily be added, seem to afford a fair presumption that scurvy may occasionally arise from the use of spoiled (decomposed) food; still, it is clear that only a small fraction of all the cases of the disease are actually due to this cause.

Scurvy has also been attributed in many instances to the use of *bad drinking-water*. Of course, no evidence on this point is valid unless the action of other causes, such as defects in diet, and other noxious agencies, can be excluded. This condition seems to have been fulfilled, however, in some quite recent observations, and we cannot but regard, therefore, the practice long observed in the English marine, of keeping the drinking-water in iron casks, as far from being an illusory safeguard against the disease. On the other hand, it is quite certain that even the best drinking-water affords no absolute protection, as is shown by the fact that in the majority of individual cases, as well as epidemics, the quality of the water has been all that could be desired.

The possibility of the not very infrequent occurrence of scurvy in consequence of the use of bad drinking-water seems to be supported particularly by the experiences during Burke's exploratory expedition to the interior of the Australian continent (Beckler[1]). While the division of the expedition to which Beckler himself belonged was severely attacked by scurvy in spite of the ample stock of provisions with which the party was supplied, the other expeditions, which were less completely equipped in this respect, escaped entirely—even the two columns

[1] Ueber das Auftreten und den Verlauf des Scorbutes im Innern von Australien Berliner med. Gesellschaft. I. H. 2. S. 211–240).

which set out later, and were obliged to subsist entirely upon the remains of Burke's provisions. The only drawback with which Beckler's column had to contend on its journey was the bad drinking-water, whereas the later travellers, in consequence of the setting-in of the rainy season, found everywhere a good supply of pure water. Beckler, therefore, attributes the cases of scurvy which occurred in his party to the bad quality of the water used on the journey.

By still other authorities many outbreaks of the disease, particularly those which have occurred in prisons and ships, have been ascribed to a certain *monotony or lack of variety in diet*, that is, to the prolonged use of certain articles of food, some of which, it is asserted, have a *direct power to induce scurvy.* This has been supposed to be the case particularly with the *salt meats*, which, in connection with the dried leguminous vegetables, form even nowadays a large part of the regular "sea-diet," and in former times were used daily for weeks and months during the long sea-voyages, to the almost complete exclusion of fresh meats. The frequency with which violent outbreaks of scurvy occurred at sea in connection with such a diet, and rapidly disappeared after the reception of fresh provisions, naturally led to the opinion that the usual sea-diet, and especially *salt* meat, contained a *pathogenic* scurvy-producing *substance.*

The history of nautical enterprises, especially those of former times, abounds in instances of the occurrence of scurvy after long-continued use of a sea-diet. Among the more recent cases of this kind may be mentioned: the outbreak of the disease in the American blockading squadron during its cruise in the Gulf of Mexico in 1846, when the supply of fresh provisions failed to such an extent that the crew of the Raritan received small allowances of fresh meat and vegetables only nineteen times in three hundred days (Foltz);[1] also the outbreak of scurvy in the Austrian corvette Dandolo during its detention in the same waters in 1865, when it was prevented from landing on account of the prevalence of yellow fever on shore, and was therefore unable to renew its stock of fresh meat and vegetables (Duchek). Another interesting instance is mentioned by Rose,[2] of a coast trader who became severely affected by scurvy, apparently in consequence of living for a long time exclusively upon salt meat.

[1] American Journal of Med. Sciences. 1848. [2] The Lancet. 1867. May.

Formerly, the opinion was very generally entertained that such a *positively* morbific substance was to be found in the large quantities of *common salt* contained in salt meats, and that scurvy arose from the excessive ingestion of this article into the blood and humors of the body. The untenability of this view was, however, soon demonstrated by two facts: 1. The frequency of scurvy in persons who had not eaten salt meat or salted provisions to excess; and 2. The circumstance that the long-continued use of large quantities of common salt has almost uniformly failed to develop the disease (Lind, Budd, Hirsch, Duchek, and others).

Widespread epidemics of scurvy, which were clearly unconnected with the use of salt food, particularly salt meat, have been frequently observed; thus, in Hungary (1735) among the soldiers of the imperial army, who were abundantly supplied with fresh meat; also in Lord Anson's expedition, shortly after the departure from the Mexican coast (1747); in the Milbank penitentiary at London (1823); in Rastatt, among the Austrian garrison (1862); in Paris during the siege of 1871; and in Ingolstadt, among the French prisoners of war (1871), etc. That an excess of salt in food is incapable of inducing the disease is shown by the absence or comparative rarity of scurvy in many northern communities, in which all the meat or fish eaten for months together has been taken in a salted condition—as well as by the absence of the disease among workmen in salt-works and salt-mines. These and similar observations have for some time past led to the almost complete abandonment of the "salt theory" of scurvy, but lately this explanation has been revived by some pathological experiments of S. Stricker and Prussak.[1] According to these investigations, a sort of hemorrhagic diathesis may be developed artificially in frogs by the injection of a large quantity of a solution of salt into the circulation, since after this operation the uninjured capillaries permit a diapedesis of the red blood-corpuscles. Cohnheim has, however, pointed out the fallacy of applying this observation to the genesis of scurvy, by showing that this hemorrhagic diathesis in frogs is a very common occurrence at certain seasons of the year entirely independently of such experimental procedures.

The evident failure of the "salt theory" to explain the notorious connection between a sea-diet and scurvy naturally directed attention to the view now generally accepted, viz., that these, and possibly *all* cases of the disease, are due, not to the toxic action of any particular ingredients of the diet, but directly to the *absence of certain substances* which are necessary to the

[1] Wiener acad. Sitzungsberichte. 1867. LVI.

maintenance of health. According to this modern theory, therefore, scurvy is to be regarded as a *special form of partial inanition*, which can be clearly shown in very numerous instances to be induced solely by the *withdrawal of fresh vegetables* from the daily diet.

Indeed, the evidence that this factor has had far more influence than any of the others previously mentioned, in the causation of most of the land and sea epidemics of scurvy, seems to be quite decisive. For the number of cases in which the disease has broken out on ships, in besieged cities, and under other circumstances, at the very time when the stock of fresh vegetables, particularly *green vegetables* and *potatoes*, began to give out, and it became necessary to rely exclusively upon bread, biscuit, rice, and dried beans and peas, is now so extremely large that the importance of this mode of causation may now be regarded as beyond reasonable dispute. Some writers, especially A. Hirsch, even go so far as to hold that the *absence of fresh vegetables* (greens, salads, potatoes) *is the sole cause of the disease*, basing their opinion not only upon the notorious frequency of scurvy at times when there is a deficiency or entire absence of these articles of food, but also upon the further fact that such outbreaks almost always rapidly disappear as soon as it becomes possible to obtain a supply of fresh vegetables, as, for instance, on the arrival of the ship in port, after the raising of the siege, etc. Whether, however, we are justified in assuming so exclusive a causation for the disease, seems to us very doubtful for reasons which we shall give later; still, we are entirely satisfied that the lack of fresh vegetables is in countless cases the most important, and in many the exclusive cause of the disease.

The abundant historical evidence upon this point has been collated so fully by A. Hirsch that we refer the reader to his summary[1] for the older observations, and content ourselves with citing a few of these instances merely by way of a historical transition to the analogous experiences of the present day. Thus, a lack of fresh vegetables was notoriously the cause of the outbreak of scurvy in Admiral Hossier's expedition to the West Indies (1726), in Lord Anson's to Cartagena (1741), and in Kane's second polar voyage. So also, according to Cartis, an outbreak occurred in 1871 in the English squadron on its way to the East Indies, when after the passage

[1] l. c. S. 546–550.

of the Cape the supply of succulent vegetables had given out, and the crew refused the pickled cabbage that was left; whereas the disease disappeared again entirely after an abundance of fruits and vegetables had been taken on board at the island of Johanna. Similar instances are to be found in great numbers during the present century: for instance, the outbreak on board the Lismoyne, bound for the Indies (1853), when only those sailors were attacked who had exchanged their daily allowance of potatoes for salt meat (Morgan); also on board the Palinurus, on her voyage to the north-eastern coast of Africa with an ample supply of good water, fresh meat, and dried vegetables (legumes and rice), but no fresh vegetables or succulent fruits. Numerous outbreaks of scurvy on land are also traceable to the same cause. Among those which occurred in former times may be mentioned particularly the epidemic during the siege of Thorn by the Swedes (1703), attributed by Bachstroem expressly to the absence of vegetable food; also the outbreak at Bremen (1762), among the English soldiers, when vegetables were no longer procurable in the markets; in recent times also the epidemic which occurred in Southern Russia (1823), after the destruction of vegetation by locusts (Lee), the outbreak at Prague (1843), after the total failure of the potato crop (Cejka), etc. As regards the endemic occurrence of scurvy, the peculiar distribution of the disease among the population of Finnmark (the northern portion of Norway) supplies us with striking evidence upon the point in question. Thus, while the disease is of very common occurrence among the Quaens and Northmen, particularly in winter, it is quite unknown among the Lapps and Finns—the only difference in mode of life being that the former live in the winter almost entirely on meat, while the latter consume, prepared with milk, large quantities of sorrel gathered in the autumn (Walter). At the conclusion of his thorough and very instructive exposition, Hirsch devotes a few remarks to the explanation of the historical fact that land scurvy has steadily decreased in frequency for the past two centuries. In accordance with the present theory, of which he is a strict adherent, he ascribes this fact to the improvements in our means of intercommunication, which enable us to rapidly supply with vegetable food any district that may have been deprived of the same by reason of a failure of the crops, or other causes. Still another circumstance which must have exerted considerable influence in former times upon the development of the disease, is the little attention which was then paid to horticulture, particularly the cultivation of green vegetables; in fact, until within a comparatively recent period, these articles of food, which we now regard as the most efficient antiscorbutics, rarely entered into the diet of the greater portion of the European population. As an instructive illustration of this fact, Hirsch mentions that in the sixteenth century, Catharine of Aragon, the consort of Henry VIII. of England, was unable to obtain a salad without sending her gardener to the Netherlands for it!—Furthermore, the very general use of *potatoes* as an article of food among the poor and rich alike, has undoubtedly contributed largely to the prevention of the disease as a popular scourge during the past two hundred years, since the affection has notoriously decreased in frequency in direct proportion to the more common use of this vegetable (Garrod, l. c.), and in fact has not occurred as a pandemic within

the past forty years, except when there has been a widespread failure of the potato crop, as was the case in the previously mentioned outbreak at Prague in 1843.

The evidence already given is certainly sufficient to establish the great, if not decisive, importance of an absence of vegetable food in the causation of the *majority* of individual cases as well as epidemics of the disease, but it may be interesting to note also how clearly the most recent observations point to the same conclusion. For instance, during the siege of Paris by the German army in 1870–71, the influence of a lack of fresh vegetables in the daily diet of the besieged was strikingly shown in the appearance of a widespread epidemic of scurvy. Thus, Delpech states that in the military hospital "du Gros-Caillou" scurvy began to show itself as soon as the supply of green vegetables and potatoes disappeared from the hospital dietary. So also, in the penitentiary in the Rue de Santé—a healthily located and well-managed institution in other respects—scurvy occurred after the 23d of September, when fresh meat, and above all, green vegetables and fresh potatoes, could no longer be obtained. That the deprivation of such vegetables is far more efficient than the lack of fresh meat in the production of scurvy is convincingly shown by numerous cases of the disease in persons who belonged to the better classes, and had been well supplied up to the end of the siege with every kind of food, except fresh vegetables. A case reported by Delpech is very instructive on this point. The patient was a wine merchant forty-five years of age, who lived in a healthy, dry, well-heated house, and was abundantly supplied with fresh (horse) meat, but about the middle of February, 1871, was attacked by scurvy. The only defect in his mode of life to which the disease could be traced was the "lack of all fresh vegetable food, particularly potatoes," ever since the beginning of the siege. The patient rapidly recovered after vegetables (dandelions, cresses) and succulent fruits (lemons, oranges) were ordered as a part of his daily diet. Similar outbreaks in the Hôpital Cochin are also reported by Bucquoy, who was convinced that all the cases observed by him were due solely to the deprivation of certain articles, especially green vegetables and potatoes. Finally, Legroux and Lasègue, who watched the course of the disease in the civil prisons of Paris during the siege, although they do not ascribe the same cardinal importance that Delpech does to the lack of these vegetable substances as a cause of scurvy, at all events came to the conclusion that the outbreaks in these various institutions (Mazas, Dépôt des Condamnés, Maison de la Santé, St. Lazare) did not take place until during the second half of the siege, when, after fresh meat had become scarce and green vegetables had given out entirely, the prisoners were also deprived of their daily allowance of potatoes. Some of the French writers on this epidemic at Paris have given also the details of certain other analogous outbreaks which have occurred within late years. Thus, Delpech describes an extensive epidemic which took place among the French soldiers during the siege of Sevastopol, in consequence of the destruction of all the green vegetables in the neighborhood of the camp by the excessive heat. A severe outbreak occurred also in January, 1867, on the French man-of-war Castiglione, during her return voyage with French troops from the unfortunate Mexican expedition. While the other vessels of the fleet, which were well provided with

fresh meat and vegetables, as well as potatoes, escaped the disease entirely, the crew of the Castiglione, who had plenty of fresh meat, but no fresh vegetables, suffered severely. The outbreak soon disappeared, however, after the neglect was repaired at the Azores.

In view of this long array of evidence, pointing clearly to the important rôle which the deprivation of certain articles of food (in a lesser degree even fresh meat, but far more especially green vegetables and potatoes) plays in the genesis of scurvy, it naturally becomes of the highest importance to inquire into the *physiological value* of these alimentary substances, or, in other words, into the *particular way in which the pathogenic effect of their withdrawal can be explained chemically.* When attention was first directed to this question, a special anti-scorbutic action was attributed to the *vegetable acids* which are well known to exist in large quantities in many vegetables, and particularly in the succulent fruits; in fact, these acids were even employed in a pure state both as prophylactics and as remedies for the disease, but the results were so unsatisfactory that the attempt to explain the effects of the so-called scorbutic diet by the absence of these substances is now very generally abandoned. Furthermore, the fact that one of the most efficient of anti-scorbutic foods, viz., *potatoes*, contains *no* vegetable acids at all, renders it highly improbable that the prophylactic virtues of the acid fruits and vegetables are directly due to the organic acids found in these substances. These considerations directed the attention of Garrod (l. c.) in 1848 to the very large quantities of *carbonate of potash* contained in potatoes, and on analyzing the articles of food most commonly in use he came to the conclusions:

1. "That in all scorbutic diets (salt meat, dried leguminous vegetables, rice, bread, etc.) potash exists in much smaller quantities than in those which are capable of maintaining health;" and,

2. "That all substances proved to act as anti-scorbutics contain a large amount of potash" (thus, besides potatoes, fresh green vegetables and salads, and also fresh meat as compared with salt meat, etc.).

This theory of the disease, according to which *scurvy is developed by the use of food deficient in potash*, has been

adopted more or less unreservedly not only by Garrod himself, but also by quite a number of eminent authorities, J. v. Liebig, A. Hirsch, and others.

On account of the importance of the subject, we give below Garrod's analytical table as rearranged by Duchek [1] to show the proportions in descending order:

	Carb. potass. per ounce.
Boiled potatoes (large)	1.875 grm.
Raw potatoes (small)	1.310 "
Lemon juice	0.852 "
Lime juice	0.846 "
Unripe oranges	0.675 "
Boiled mutton	0.673 "
Raw beef	0.599 "
Boiled salt meat (slightly salted)	0.572 "
Peas	0.529 "
Raw salt beef	0.394 "
Small onions	0.333 "
Best wheaten bread	0.258 "
Dutch cheese	0.230 "
Best wheat flour	0.100 "
Oatmeal	0.054 "
Rice	0.010 "

As regards fresh vegetables, which are omitted from this list, it is to be borne in mind that the potash, most of which is combined with the organic acids, is much more abundant in all parts of green plants during their period of vigorous growth than later when the leaves are fully formed, and that on the other hand the amount of lime and silicic acid, which is at first small, afterwards steadily increases (J. v. Liebig).[2] Moreover, since the salts of the vegetable acids are known to be all converted in the body into carbonates, it is clear that the ingestion of the potash salts of the vegetable acids must be nearly, if not completely, equivalent in its final effect to the direct introduction of potash. The behavior of the phosphate of potash, chloride of potassium, and nitrate of potash, which are largely found in fresh meat, dried leguminous vegetables, etc., is, however, somewhat differ-

[1] Handbuch von Pitha und Billroth, l. c. S. 285.

[2] Die Chemie in ihrer Anwendung auf die Agricultur und Physiologie. 9. Aufl. 1875. S. 203.

ent; these salts are not converted into carbonate of potash, but pass through the body for the most part unchanged. This very circumstance, as Chalvet has pointed out,[1] interferes with their perfect assimilation, whereas the potash associated with the vegetable acids readily escapes from its loose alliance, and is therefore more available as formative material for the various tissues of the body (particularly the muscles, red corpuscles, etc.). These hints in regard to the physiological rôle which the retained potash plays in the body, as well as in regard to the pathogenic effects which a deficiency or complete lack of this material in the food may be supposed to produce, must suffice at present; but we shall refer to the subject again later in the article (see Nature of the Disease).

Although we must admit that Garrod's theory of a deficiency of easily assimilable potash salts in the food as the real efficient cause of scurvy seems in a high degree attractive and entirely adequate to account for a very large number of observed facts, such as the frequent outbreak of the disease after the prolonged use of the so-called sea-diet on shipboard and during long sieges, we are still not prepared, without further evidence, to regard this explanation as applicable to all the individual cases of the affection. Indeed, if we are not to do violence to known facts, the hypothesis in question seems to us to require restatement in the following modified form, viz., that while as a rule a diet deficient in easily assimilable potassium salts (especially potash) appears to result sooner or later in the development of scorbutic symptoms—and the more rapidly and certainly in proportion as this factor is aided by certain other noxious agents to be mentioned later—on the other hand, *scurvy notoriously occurs in very numerous instances when there has been no deficiency in the supply of potash*. In fact, it is not more certain that a lack of easily decomposable potash compounds in the food is decidedly the most effective cause in the majority of scurvy epidemics, than it is that not only individual cases, but even widespread outbreaks of the disease, may develop independently of this connection.

[1] Soc. méd des hôpit. Séance du 24 mars, 1871. Gaz. hebd. 2. S. T. VIII.

Among the more recent epidemics which were clearly *unconnected* with a deficiency of fresh vegetables, may be mentioned particularly the one at Rastatt in the winter of 1851–52, to which we have before repeatedly referred. Notwithstanding the use of fresh vegetables, so far as the season of year permitted, six hundred and ten of the Austrian garrison of the fortress were attacked with scurvy, and it was particularly noticeable that, although the epidemic began in November, the great majority of cases occurred in May and June, a season of the year in Southern Germany when fresh vegetables are always abundant. The monthly list of patients was as follows:

November, 1851	1	April, 1852	87
December "	0	May "	187(!)
January, 1852	1	June "	243(!)
February "	3	July "	56
March "	20	August "	12

So also with respect to the origin of the scurvy which appeared among the French prisoners of war confined at Ingolstadt in 1871, Doering expressly states that the dietary contained an ample allowance of meat and potatoes, and that on this occasion, at all events, the disease was not traceable to a lack of vegetable food. A similar report was made some time before this (1825) by Seidlitz, in one of the papers of the St. Petersburg physicians, in regard to the occurrence of scurvy among the inhabitants of Astrakhan. This writer showed that the disease usually continued to spread in this country up to the middle of May, although plants and vegetables of all kinds were abundant after the first of April, and were used daily by the people in large quantities (cresses, dandelions, salad, chiccory, spinach, sorrel, lettuce, parsley, onions, garlic, etc.). Furthermore, Rochoux remarks, in reference to the distribution of the disease among seamen of different nationalities, that Indian sailors, who live exclusively upon vegetables, are subject to the disease; still, the force of this objection to the above theory is broken by the fact that rice, which forms the chief vegetable food of these persons, is characterized by a marked deficiency of potash (see the table previously given). Still more striking evidence is afforded by the outbreak which occurred on the Austrian frigate Novara, during her voyage from Madras to Singapore, although the daily diet contained not only fresh meat, but also bananas, lemons, oranges in large quantities, cocoanuts, yams, etc. (Schwarz); also by Duchek's observation that in Lemberg scurvy prevailed more especially among the poorer part of the population, who lived almost entirely upon vegetable food, particularly potatoes. These and the numerous similar instances to be found in the history of scurvy certainly show this much, that Garrod's theory, however high we may estimate its importance for the explanation of *many* scorbutic affections, is by no means adequate to solve the etiological problem in *all* cases of the disease.

Among the other influences which appear to bear a causal relation to the disease, either as factors auxiliary to the dietary

defect discussed above, or as direct and independent causes in themselves, may be mentioned particularly:

1. *Unhealthy dwelling apartments.*—The frequency with which scurvy occurs among individuals compelled to reside for a long period in *cold*, *damp*, *poorly ventilated* and *lighted rooms* (cellars, casemates, and prisons), is one of the best attested facts in the history of scurvy. In many of these cases, of course, the result has been largely due at the same time to the lack of proper food; still, instances are not wanting in which the direct agency of the factor in question could be isolated with a fair degree of certainty—as, for instance, when, under the same conditions of diet, the disease has selected from a given body of men only those whose dwelling apartments were unhealthy, or an outbreak has rapidly disappeared after the removal of the patients to better quarters.

An instructive illustration of this mode of origin is presented by the Rastatt epidemic, which has already been mentioned in another connection. Although the troops at this fortress all had the same diet, the Austrian garrison, which was quartered in a narrow, damp casemate, and was obliged to do arduous guard duty by the side of the wet trenches, suffered severely from the disease, while the Baden guard for the convicts escaped almost entirely. A similar immunity was noticeable also among the officers of the Austrian garrison, who occupied better ventilated and less crowded rooms in the casemate, while their food and out-door exposure were essentially the same as those of the rank and file (Opitz). Still clearer evidence is afforded by the epidemic in the military prison at Alessandria (1844), where only the convicts confined on the *lower* damp floor were attacked, while those occupying the *upper*, dry and better ventilated floor, remained free from the disease, although the diet was exactly the same in both cases.[1] So also the epidemic which broke out in the damp, too much shaded military hospital at Givet (May, 1847), was ascribed by Scoutetten [2] to the unhealthy situation, since the disease disappeared soon after the patients were transferred to a more elevated locality in the neighborhood. Doering gives a similar explanation of the recent epidemic among the French prisoners of war at Ingolstadt, where the diet was in every respect unobjectionable, and no cause could be assigned for the outbreak, except the confinement in the narrow, damp casemates of the fortress. Similar facts in considerable numbers may be cited from the history of scurvy at sea; for example, where among the vessels of a fleet—all provisioned alike—scurvy appeared only in the one whose quarters for the crew were obviously unhealthy. Thus, during Cook's second

[1] *Novellis*, Annal. universal. 1845. Nov.

[2] Gazette méd. de Paris. July, 1847.

voyage of discovery, a violent outbreak of scurvy occurred on the Adventure, while the other vessel, the Resolution, escaped entirely. The diet and amount of work were the same on both vessels, and the only difference to which the attack could be attributed was the fact that the Adventure sailed deeper in the water than the Resolution, and was obliged to keep her hatches closed during stormy weather, so that it was impossible to keep the quarters below decks properly ventilated. These and similar experiences on land and sea naturally raise again the question touched upon at the outset of this chapter, whether the disease may not possibly be due in *many* of the epidemics to a specific miasm which develops in, and attaches itself to, certain localities; but, as we were obliged to admit on that occasion, our information is still too incomplete to warrant an absolute decision upon this point.

2. *Unfavorable meteorological conditions.*—The *temperature* and *degree of moisture of the atmosphere*, as modified particularly by the *season of the year* and the *climate*, appear also to exert some influence upon the development of the disease. Thus, it has generally been noticed that in temperate latitudes land epidemics occur much more frequently during continuously *cold, damp weather*, and, therefore, especially during the *inclement season of the year.* This fact is shown very strikingly by Hirsch's compilation of all the known extensive epidemics; for out of the sixty-eight land outbreaks twenty-one occurred in winter and thirty-seven in spring, while during the summer and autumn there were only eight and two respectively. At *sea* also this predilection of scurvy for a continuously *cold, moist climate* has been perhaps even more conspicuous than on land. Thus, for the higher latitudes we need mention only the well-known frequency and extreme severity of the disease on polar expeditions and on whaling vessels sailing in the northern seas, while even in the temperate zones there are certain regions of the ocean where storms and rainy weather are so habitual (*e. g.*, the waters in the neighborhood of Cape Horn), that before the introduction of steam navigation sailors regarded these localities as the fixed quarters of scurvy, in which it behooved every sailing vessel to tarry as short a time as possible. That there is, therefore, a certain causal connection between these meteorological conditions and scurvy, can hardly be questioned, but whether the relation is a direct and immediate one is very doubtful; far more probably, at least in the great majority of cases, it is of merely an *indirect* nature, and dependent upon the difficulty of obtain-

ing proper vegetable food in cold climates or during the inclement season of the year. This view is supported by the fact that violent outbreaks of scurvy have repeatedly occurred under directly opposite conditions of temperature and moisture, that is, during continuously *hot* and *dry* weather; for instance, when the vegetation throughout a large region of country has been blighted by drouth and fresh vegetables are no longer to be obtained, as well as when sailing vessels are becalmed in tropical seas for days and weeks at a time, and the supply of potatoes has gradually given out. Still, while the influence of cold and moisture in the genesis of scurvy is, upon the whole, therefore, rather indirect than immediate, it would be incorrect in our judgment to insist that these factors have no direct agency at all. For, in view of the familiar experience that the body demands an increased supply of food during cold, damp weather, in consequence of the greater loss of heat and more rapid waste of the tissues at such times, it is *à priori* not only possible, but even very probable, that any limitation of food, particularly of those substances the lack of which is known to produce scurvy most readily, will *ceteris paribus* be most likely to induce the disease when there is the greatest disproportion between the demand for food and its supply. It is clear, therefore, that cold and moisture, although not "efficient causes" in the strict sense, are still important auxiliary factors in the etiology of scurvy, increasing to an important degree the effect of improper alimentation, and in the minor grades of incomplete nourishment even acting as the immediate determining cause of the outbreak.

3. *Excessive physical exertion* or a *lack* of *proper exercise*. That *severe bodily exertion* promotes in a high degree the development of scurvy, especially when there has been no corresponding increase in the allowance of food, may be fairly inferred from the results of very numerous observations. Thus, on shipboard the disease has repeatedly been noticed to break out at times when the crew were compelled by severe weather to keep on duty day and night without any extra allowance of rations. Similar instances have often occurred also in prisons, on occasions when the prisoners had been employed for a long time at hard labor on earthworks, buildings, etc., and the same diet had

been used as when the prisoners were kept at rest. In army epidemics also it has been noticed that the disease is specially apt to attack the soldiers whose duties are the most arduous. Still more convincing are the numerous instances in which, during sieges, the military garrison intrusted with the defense were exclusively attacked by the disease, or at least were affected in far greater proportion than the citizens whose allowance of food was exactly the same. It is highly probable, therefore, that fatigue renders the body specially susceptible of scorbutic disease in much the same manner as cold and moisture seem to do, viz., by increasing the waste of bodily substance, and thus hastening and accentuating the pathogenic effects of insufficient or improper food.

During the violent outbreaks of scurvy at the siege of Thorn (1703), the epidemic began among the Saxon garrison, and did not extend to the citizens until towards the end of the siege, when, in consequence of the almost annihilation of the garrison by the scourge, the citizens themselves were obliged to stand guard and perform other military duties (Baehstroem). In 1841 Cannstatt observed an outbreak of scurvy in several squadrons of the Bavarian light cavalry, whose duties had been unusually severe, while their diet was insufficient; Wolfram,[1] moreover, mentions that out of the fifty-six scorbutic cases in the garrison at Lille in 1860, no less than forty-four were artillery drivers—soldiers, therefore, who, upon the smallest pay and with the same rations as their companions, had been kept hard at work taking care of their horses from four o'clock in the morning in summer and five in the winter, up to seven in the evening. In general, scurvy seems to select the cavalry in preference to the other branches of the service (Cannstatt, Duchek), probably on account of the longer daily duty required of mounted soldiers. As another illustration of the influence of severe labor with insufficient diet may be mentioned also the outbreak reported by Wald, in the prison at Wartenberg, in 1854. On account of the overcrowding of the Prussian prisons it became necessary to enlarge the building at this place, and all the convicts except the feeblest were employed on the works, without any change in the usual diet, which was composed chiefly of bread and leguminous vegetables, until the occurrence of a violent outbreak of scurvy in August taught the authorities the necessity of repairing the neglect by adding meat, milk, and green vegetables to the daily rations. The same mistake of keeping laboring men upon a diet adjusted to a state of repose was committed two years before this time, in 1852, in the Prussian prison Ravicz, where the prisoners were employed, without any dietary precautions, as laborers in the reconstruction of the burned portion of the building, and in consequence suffered from

[1] l. c. S. 152.

an outbreak of scurvy. A similar outbreak was recently observed by Duchek among the workmen in Klosterneuburg (1868), who, although working twelve hours a day in close rooms, had lived upon the same food as when they were entirely inactive. In this connection we may mention also the remark of Lord Brougham in the House of Lords (Sept. 27, 1841), that eleven and a half per cent. of the persons confined in slave-ships and English prisons were reported as suffering from scurvy as a result of overwork upon an entirely insufficient diet.[1]

On the other hand, *want of exercise* is also said to predispose to scurvy (Krebel). Thus, it is asserted that sailors who take sufficient exercise to keep up a good appetite and active digestion, so as to properly assimilate the usually very indigestible food which forms their diet at sea, are much less apt to suffer from the disease than their lazy companions whose appetites and digestive powers have become impaired by an indolent mode of life. This greater predisposition to scurvy on the part of such individuals is doubtless connected with the derangement of assimilation induced by their sedentary habits, whereby the tissues become imperfectly nourished and less able, consequently, to resist morbific influences in general.

4. *Mental depression.* Among the influences which contribute to the development of scurvy may be included, finally, the mental emotions, especially long continued *anxiety* and *despair*, and perhaps even *ennui;* while, on the other hand, joyful emotions are said to have a favorable influence upon the course of the disease in individual cases as well as in entire epidemics. Of course the external conditions under which scurvy has usually occurred —wars, sieges, difficult nautical expeditions, confinement in prisons and hospitals, etc.—are peculiarly adapted to call forth the depressing emotions; and it is certainly not unlikely, from what we know of the injurious effects which such emotions exert upon the vegetative functions of the body, that the mental disturbances thus occasioned may have played, to a certain degree, an *active* and *independent* part in the genesis of the disease. Still, it has never been possible under such circumstances to isolate this influence, or to accurately determine its importance, since very generally the causes of the mental depression were the same as those to which the development of the scurvy could

[1] *Krebel*, l. c. p. 213.

also be ascribed. The same difficulty presents itself in estimating the importance of joy, reawakened hope, and other elevating emotions in favorably influencing the course of the disease. That such an influence is actually exerted, and is not merely apparent, can hardly be questioned. For instance, Blane states positively that in the English men-of-war outbreaks of scurvy have usually subsided rapidly after victorious engagements. Still, in most cases these elevating emotions and the disappearance of the scourge are really but *co-ordinate* effects of the same *fundamental cause*, viz., the favorable change which has occurred in the external situation of the individuals, as for example, through the raising of a long siege, or the final arrival of the vessel in a safe harbor where a supply of provisions could be obtained, etc.

It must be evident now, we think, from a retrospective survey of this abundant material which has accumulated in the course of time in regard to the etiology of scurvy, that we have failed to obtain a uniform theory, or, in fact, any perfectly clear conception of the genesis of the disease. Not only does the affection seem to arise in *different ways in different cases*, but even where we have had more or less positive evidence of the direct agency of certain noxious influences, such as those mentioned above, we have not always been able to point out their mode of action with absolute precision. In a subsequent chapter, after we have considered the symptomatology and morbid anatomy of the disease, we shall return to the results of our etiological inquiry, for the purpose of applying them, so far as is feasible, to an interpretation of the pathological process and its clinical manifestations. But for the present we may conclude here with the following summary of the conclusions—negative and positive—which we have thus far reached :

1. Scurvy is certainly not a contagious disease.

2. A miasmatic mode of origin is likewise clearly to be rejected for the majority of cases, but in many instances cannot be excluded with absolute certainty.

3. In many cases scurvy seems to be produced by the use of spoiled food and bad drinking-water.

4. The excessive use of salt is not an efficient cause of scurvy.

5. The majority of cases of scurvy are most probably due

directly to a deficient supply of certain nutritive substances, which are more abundant in fresh than in salt meat, and are particularly abundant in green vegetables and potatoes.

6. It is probable that the immediate cause of scurvy in most instances is a deficiency of potash in the food, especially the potash salts of the vegetable acids.

7. An absence or deficiency of antiscorbutic food seems to produce the disease more readily when the demand for food is for the time being increased by external conditions (cold, damp weather, hardship), or when the vegetative functions are impaired by depressing influences of all kinds (lack of exercise, mental emotions, etc.).

8. There are, therefore, auxiliary causes of scurvy, and it is not improbable that these influences, when they are specially potent or when several of them act in combination, may sometimes develop the disease in individuals or masses of men without the presence of the usual cause (the Rastatt epidemic, etc.).

Pathology.

General Description of the Disease.

The beginning of scurvy is, as a rule, slow and gradual, and manifests itself for the most part by symptoms which at first do not bear the characteristic stamp of the later local phenomena of the disease, but are decidedly of a more general and indeterminate nature. These less pathognomonic changes in the general condition, as they usually appear at the very beginning of the disease, do, however, belong to the scurvy itself, and not to some prodromal cachexia of another kind; since observation of the malady in its fully developed form teaches plainly that that initial general malaise lasts, without any material change, during the whole continuance of the scurvy—indeed, that it increases in intensity proportionally to the subsequent development of the localized symptoms. If this then constitutes an integrant part of the attack of scurvy, it must, on the other hand, be allowed that there are also cases of scurvy in which the disease seems

to appear at once with the development of local foci, without serious initial general illness, and it is only later that the alteration of the general condition shows itself more plainly (Cejka). Yet such cases form decidedly the minority, and even in these the cachexia, as was just noticed, usually does not fail to manifest itself later. One may, therefore, be allowed to consider the existence of this latter, whether first developed somewhat later, or, as in most cases, constituting a characteristic feature of the disease from its very beginning, as a peculiarity which almost constantly belongs to scurvy, or as an essential criterion of the *pathological species* (comp. Diagnosis).

The evidences of this developing *cachexia* are, briefly stated, the following: Those attacked begin to complain of great *weariness* and *depression*, which gradually increase to such an extent that after even the slightest bodily exertion a feeling of complete exhaustion results, coupled with a *sense of oppression* in the chest, as well as with palpitation of the heart. This lessening of the normal feeling of bodily vigor is regularly accompanied later by painful sensations in the voluntary muscles, at first with the character of the muscular pain which usually follows over-exertion of the body, but later with a more violent (rheumatic-like) character. These sensations annoy the patients principally in the day-time, and especially after rather active movements; during the night, on the contrary, as well as after long repose in bed, a temporary alleviation is often experienced. The pains are sometimes very variable as to locality, and then usually visit just those groups of muscles which were in activity shortly before; sometimes, however, they are more fixed in their nature and are then localized preferably in the muscles of the small of the back and calves of the legs, which come specially into play in walking. Another pathological peculiarity of the scorbutic cachexia, which likewise often makes its appearance at an early stage, is the patient's great *sensitiveness to a low temperature*, in consequence of which he is very apt to complain of feeling chilly and manifests a disposition to seek warmth (for instance, in bed). Together with these sometimes painful, sometimes merely uncomfortable sensations, there exists further, in most cases from the very beginning, a noticeable need of sleep, to which even in the day-

time the patient is often compelled to yield, without experiencing, however, a corresponding degree of refreshment. Furthermore, during their waking hours the patients show a changed psychical demeanor, which is marked by increasing apathy and indolence of mind, and chiefly by a spiritless and dejected mood, which is also usually not wanting in those cases of the disease in which the psychical depression is not fully explained by the wretched surroundings of those attacked (comp. Etiology). In regard to the *need of food*, individual cases of scurvy behave at the beginning of the disease quite differently. In some cases, for instance, the appetite disappears at an early stage, while in others it lasts longer, and may even in individual cases degenerate into a positive voracity, characterized perhaps by a strong craving only for acid food. At other times all articles of food within reach of the patient, even though repulsive and decomposed, are gulped down with a greed that is positively unearthly. The feeling of thirst is usually not essentially changed so long as no fever exists.

Simultaneously with these subjective derangements of the general condition, the appearance of the patients is for the most part also changed. The features fall in and are marked with a painful and sad expression, the eyes especially sink back more and more into their orbits and are encircled by broad, bluish-violet rings. The reddish tint, too, of the lips and cheeks gives place to a more cyanotic hue, and the mucous membrane of the mouth shows the same change in color. From day to day the skin shows an increasing pallor and earthy color, and in a few cases we may find, even in this prodromal period, brownish-colored spots of greater or less extent, with ill-defined outlines, on various parts of the face and body (Opitz) similar to those of bronzed-skin. The spots, once developed, generally outlast the hemorrhages and ulcerations of the skin which occur at a later date; and in those cases which terminate favorably, they generally lose their color only during convalescence. Another much more constant skin-symptom, which, moreover, hardly ever seems to fail when the disease is at its height, and as a rule is noticeable even in the prodromal period, is the remarkable dryness and brittleness of the epidermis, which is thrown off in scales like bran (pityriasis tabescentium). Still another characteristic pecu-

liarity is the greater prominence of the follicles on the otherwise withered and flaccid skin, a peculiarity which will be most readily recognized by passing the hand over the extensor side of the extremities (Duchek). The temperature of the skin appears to the touch rather lessened than increased, but whether the inner temperature of the body experiences feverish augmentation at the very beginning of scurvy is more than doubtful, although for that matter accurate thermometrical observations of this period of the disease are wanting. It is, however, by no means probable that any increase of temperature of the body which might occur at this time could reach the degree of febrile movement often observed at a later stage.

Besides the morbid changes just mentioned in the appearance and the condition of the skin, there will be observed, for the most part quite early, and often before the breaking out of the real local scorbutic symptoms, signs of a *disturbed*—that is, of an *impoverished general condition of nourishment;* the heart's action, too, will be found to be feebler than natural. The muscles of the body lose their previous normal firmness, become flaccid and somewhat emaciated; there is likewise generally to be observed, even at this early period, a moderate decrease of the panniculus adiposus, and therefore a corresponding decrease of the weight of the body. The arterial pulse becomes smaller and softer, and the contractions of the heart diminish in frequency. It is only after bodily exercise, as in persons suffering from anæmia, that a more vigorous action of this organ manifests itself temporarily—this increased vigor being perceived by the patient as a feeling of palpitation, and by the physician as a more frequent and more vehement impulse of the heart. The frequency of respiration, which during repose is, as a rule, not essentially changed, may likewise, by the same causes, be increased to violent panting. A thorough physical examination of the heart and lungs, as well as of the abdominal organs, shows as yet nothing abnormal. The spleen, it should be remembered, owing to previous or still existing intermittent fever, has been found enlarged in the prodromal period of scurvy; on the other hand, no enlargement of the spleen belongs properly to the disease, at least in its early stages. Just as little does

the secretion of the kidneys at the commencement of scurvy seem to undergo any decided change.

Finally, in regard to the duration of this initial period, this varies extremely, and may under certain circumstances be very long—that is, may last many weeks. Oftener, however, more decided symptoms of disease appear, even as early as during the first or second week, and lend à more serious aspect to the cachexia. The hitherto ill-defined picture of the disease assumes a more decided character, and shows the marks distinctly characteristic of scurvy. Moreover, it will be remembered that it was distinctly stated by us in the beginning that in many cases the initial stage may be only slightly developed, or even wanting altogether, and that in these, for the most part light forms, the disease is marked from its very commencement by the local symptoms which are now to be mentioned.

In the majority of all cases the existence of scorbutic disease is first proved in an unmistakable manner by the *gums*. That is to say, while usually during the prodromal period the whole mucous membrane of the mouth exhibits a bluish tinge, there is now developed on the edge of the gums, and especially on the outer side of the incisors, a zone of greater or less breadth within which the mucous membrane has a dark bluish-red tinge, and at the same time appears swelled and loosened in its connection with the teeth. All these changes are most pronounced on the pointed projections formed by the gums between the individual teeth, and which now begin to protrude more and more like puffy knobs. The swollen parts of the gums are at the same time quite painful; they bleed, too, very readily on touch or pressure of whatever kind; while, on the other hand, the rest of the mucous membrane of the mouth does not usually show abnormal sensitiveness or become at first the seat of bleeding. It is, moreover, characteristic of the scorbutic affection of the mouth at the beginning, as well as in its later stages, that, however much the painful swelling and redness of the gums may extend backwards from the region of the incisors upon the mucous covering of the eye-teeth and molars, yet all those places where teeth are wanting remain entirely unattacked; so that, for instance, in the case of chil-

dren with few teeth, or of aged persons, the scorbutic affection of the mouth is reduced to a minimum, or may indeed be entirely absent. On the other hand, in those places where only the stumps of teeth or merely the roots remain in the alveoli, the mucous membrane is attacked, just at if the row of teeth were perfect; indeed, it is precisely at such places that the affection often shows itself in an especially intense form. Finally, in proportion to the development and preponderance of the above-described changes do the patients begin to diffuse a nauseous odor, which is not at first characterized by that carrion stench usually perceived in the exhalations of those suffering with scurvy in a more severe form or at a more advanced stage.

Well-marked scurvy, however, does not invariably begin with the gums; cases also occur in which, after a shorter or longer continuance of the prodromal period, or indeed without any such, other symptoms than the characteristic affection of the mouth are first observed, and it is only later in its course that the reddening and inflammatory swelling of the alveolar edge is added to these other pathological appearances of the disease. Thus, cases have been observed in which suggilations of the skin, bloody infiltration of the subcutaneous connective tissue (especially of the lower limbs), or even hemorrhages of the bowels, preceded the affection of the gums (Cejka, Duchek, and others). It must certainly be considered as a matter of some importance, in its bearing upon the question of the origin of scorbutic manifestations in general, that quite often the first evidence of serious local symptoms, while the cachexia was still but slightly developed, occurred preferably on precisely such parts of the body as had been exposed to an injury of some sort (mechanical or chemical), or on which at some previous time an inflammatory process had existed, and had subsequently run its course.

For instance, a very slight bruise, which in the case of a person in good health would hardly leave any trace, may lead, in the case of one suffering with scurvy which is still in the latent stage, to an extensive suggilation of the skin, and with this to manifest breaking-out of the disease; or, in another analogous case, the administration of a purgative may occasion not simply a diarrhœa, but even a profuse enterorrhagia; finally, in a third case, the development of scurvy causes the

granulation tissue in a wound to become spongy and to bleed easily. In all such cases the anomaly of the beginning of the disease consists in this, that in the case of individuals who have indeed, as a rule, a certain degree of cachexia, but as yet no scorbutic affection of the gums, local appearances of scurvy may occur at first on other parts of the body, while the affection of the mouth only occurs at a somewhat later period of the disease. One circumstance, however, is common to all these cases of scurvy of anomalous commencement—namely, that a district of the body, which has been in some way injured or otherwise pathologically affected before, becomes the first seat of the disorder.

Finally, in this connection it should be stated that, in a few cases of well-characterized scurvy, this affection of the mouth is completely absent during the whole duration of the disease, and that, too, notwithstanding the presence of teeth or the remains of teeth in the jaws. This anomaly, however, belongs to the rare exceptions ; the early and almost constant complication of the gums is the rule.

Then again, there are a few cases—generally of a mild type —in which the affection of the mouth, coupled with a certain degree of general discomfort and weakness, is the *only* symptom which betrays the scorbutic nature of the disorder. In these cases, moreover, the disease may, by a timely change in the manner of life, good care, and proper treatment, be made to retrograde even at this early stage. In such an event not only does the general condition improve—the bodily and mental exhaustion of the patient giving place to a normal feeling of strength and the expression of the face becoming more natural, but the affection of the mouth also often shows a surprising tendency towards recovery. The œdematous swelling of the edges of the gums diminishes and their livid redness disappears ; the parts also cease to be painful, and show no disposition to bleed ; in a word, everything proclaims the *restitutio ad integrum* of the parts interested.

More commonly, however, the disease pursues a different course. In the more severe forms of scurvy, and sometimes also in the lighter ones, after the cachexia is fully developed and the gums show the pathological changes already described, there arise still other local lesions in districts of the body which are, in an histological point of view, widely diverse. But before we

submit these other local symptoms of the disease to a brief examination, it seems necessary to give further consideration to the changes which the general condition and the affection of the mouth undergo in the more severe degrees of scurvy.

If the case assumes a severe type, which generally then happens when scurvy attacks those already diseased or incapable of resisting it, or when the injurious causes, described under the head of etiology, continue active during a long period and can thus develop their whole pernicious influence, then the weakness and prostration of the patients soon become extreme. They are unable to walk about and cannot even sit up; and while they are in such a condition of prostration, the mere attempt to lift them into the upright position may bring on a dangerous and sometimes even a fatal fainting fit. The pulse and the heart-beats both become reduced to a minimum of strength, and on auscultation of the heart systolic murmurs may now often be heard, as in the case of the most advanced stages of simple and of pernicious anæmia. Every movement, however slight, gives rise to the painful sensation of palpitation of the heart, accompanied by dyspnœa and a feeling of great oppression. The appetite is entirely absent; the thirst, on the contrary, is as a rule increased, owing to the fever which is now almost constantly present. The rheumatoid muscular pains have also increased in intensity and rob the patients of their rest at night—in short, all the subjective symptoms and functional disturbances which were present during the initial period have now very greatly increased and reached their highest degree. From the appearance of the patients and from their general condition of nutrition, it is clearly evident that they have reached a very high degree of cachexia. The features are greatly changed; the body seems emaciated, although it shows at the same time more or less dropsical swelling, especially on the lower limbs; the skin is dry and flaccid, and the epidermis comes off in scales; in some places, too, it will be found to have lost its natural covering of hair; finally, almost always the hemorrhagic spots, presently to be described, will be found scattered over a greater or less extent of the body. This disease, really terrible in the later stages of its progress, may in individual cases of intense scurvy be devel-

oped from cases previously of a milder character, the change in type taking place sometimes very gradually, sometimes more abruptly. In the latter case, for example, the development of severe local symptoms often influences for the worse the patient's general condition in a very sudden manner.

In severe and protracted cases of scurvy the diseased condition of the gums increases both in extent and intensity in proportion to the increase of the general cachexia. The bloody and œdematous border of the gums, at first narrow, extends towards the roots of the teeth, and at the same time steadily increases in thickness. There are thus formed at last very bulky, spongy swellings, which are of an intense bluish-red color, bleed abundantly at every touch, and are for the most part very sensitive. In some cases these swellings may be so great as to completely conceal the teeth. The act of chewing, which was already difficult before, becomes now almost impossible, especially if, as is often the case, the formation of a diphtheritic slough, or a diffuse ichorous disintegration, be superadded to the inflammatory œdema of the gums. Where a diphtheritic slough has formed there will be observed along the upper edge of the gum, or on the summits of the swellings, lardaceous grayish-white deposits, which adhere closely to the mucous membrane, and when removed leave behind a bleeding excavation in the substance of the gum. On the other hand, where a diffuse ichorous disintegration has taken place, the parts present the appearance of a slimy and extremely fetid mass, which, on being cast off, is discharged from the mouth mixed with abundant mucus. Where this latter process takes place, the roots of many of the teeth are often deprived of their covering of mucous membrane; moreover, they may become loosened in their attachment to the alveoli, and finally may even fall out, after first becoming discolored and in some cases even carious. It is, however, remarkable that while in severe cases of scurvy the most serious changes always take place in the gums and teeth, the mucous membrane of the rest of the mouth participates, even at this stage, in so slight a degree. All the rest of the mucous membrane of the mouth, even when the gums are most severely attacked, shows, as a rule, only a livid color and moderate

œdema—seldom a disposition to bleed, or severe inflammation, or real ulceration.

If we pass on now to the consideration of the other local manifestations of scurvy, we shall find that *the skin*, *the connective tissue*, and *the muscles*, are, next to the mucous membrane of the mouth, the parts most often affected by this disease, as well in the mild as in the more severe forms. Eruptions of a pronounced hemorrhagic character are among the characteristic manifestations of this disorder. They are usually developed in the later stages of the disease, though not unfrequently also in the earlier ones. These purpuric efflorescences are oftenest and earliest developed on the lower extremities, but are also observed, especially in severe cases, on the rest of the body (on the trunk, on the upper extremities, but comparatively very seldom on the face or on that part of the head which is covered with hair). They occur in part without apparent cause, in part as the immediate result of an injury to the skin, often of a very trifling nature. Among the hemorrhagic eruptions which have developed spontaneously, the most numerous, as well as the most regularly found, are the small follicular petechiæ, which vary from the size of a hemp-seed to that of a lentil. These spots are of a roundish shape and at first of a dark bluish-red color ; they do not disappear on pressure, and are slightly or not at all prominent. Furthermore, as these spots are situated immediately over the hair-follicles, a hair or the stump of a hair will generally be seen rising up through the centre of each spot. The color of the spots, which at first is bluish-red, afterwards passes gradually through a variety of hues—greenish, then brownish, etc. Quite often also in cases of scurvy, elevated efflorescences will be found, of the same color and size as the simple petechiæ maculatæ. They seem to occur independently of any external cause, and many assume either the character of small nodules (Lichen scorbuticus, Lichen lividus, Acne scorbutica—Purpura papulosa), or that of small vesicles, filled with sanguinolent fluid (Herpes scorbuticus, Purpura vesiculosa). Apart from these various circumscribed forms of cutaneous hemorrhage, larger and more extensive extravasations into the tissues of the skin, and beneath the epidermis, occur much more frequently in

scurvy than in any other form of hemorrhagic diathesis. In outward form these foci of disease present at one time the appearance of extensive blotches (ecchymoses) of irregular form, colored at first violet-red, later bluish-green, brownish, etc.; at another, that of streaked extravasations of blood, or stripes (vibices); sometimes, also, that of vesicles of quite large size, filled with sanguinolent fluid (Pemphigus scorbuticus). These proruptions, the larger as well as the smaller ones, seem to occur by preference on the skin of the lower extremities. As the disease, however, advances further in its development, these interstitial hemorrhages of spontaneous origin occur also on other parts of the body. With the progress of the disease, too, the more readily does a trivial external injury produce suggilations of varying form and extent. Instances are known where a rather hard and somewhat uneven support has been sufficient to produce them in the arms; they have also been produced in the buttocks by a crease in the sheet upon which the patient lay. In severe cases of scurvy almost the whole surface of the body, except perhaps the face and head, may be covered with partly confluent, larger and smaller, newer and older, purpuric eruptions, which naturally give to the patient an appearance as variegated as it is strange and alarming.

Not always, however, do the cutaneous hemorrhages of scurvy patients appear under the clinical form of simple interstitial hemorrhages, or of simple inflammatory hemorrhagic exudations on the free surface of the corium; often the extravasation of red blood-corpuscles is only the prelude to, or a part of, more severe destructive processes which result in the formation of ulcerations of the skin. Pemphigus scorbuticus may, in the absence of all treatment, or where improper treatment is carried out, pass into a condition of ulceration of the skin—suppuration first taking place under the blackish crusts into which the vesicles have been converted, followed by a gradually progressing disintegration of the tissues of the skin (Rupia scorbutica). In cases which pursue a more favorable course, and especially if the patients receive an appropriate and timely treatment, the crusts fall off, without the skin having been destroyed beneath them, and all that remains to mark the spot is a temporary brownish discoloration.

On the other hand, the peculiar ulcers of the skin (ulcera scorbutica) which occur with remarkable frequency when the course of the disease is malignant, do not always arise in the above described manner from pemphigous eruptions, but may also in certain cases, without the previous formation of a vesicle, develop immediately from a simple hemorrhagic infiltration of the skin, which undergoes purulent breaking-down, or it may result from the breaking open afresh of recent and still highly vascular cicatricial tissue of the skin. Finally, we sometimes meet with cases, as was incidentally mentioned above, where a so-called scorbutic ulcer, with its peculiarities which will shortly be noticed, is developed by speedier or more tardy metamorphosis from an ulcer of another description already existing; this is likely to happen, for example, when the patient has meanwhile chanced to become affected by general scurvy.

Now, although we should not be justified in asserting that scorbutic ulcers of the skin possess pathognomonic characteristics—that is, characteristics which are observed only when scurvy exists—still these ulcers present features which are, to a certain extent, characteristic of the disease. These special features are more easily recognized in all those cases in which several such ulcers are developed on the patient at the same time or in quick succession, and thereafter pursue nearly the same course of development. These ulcers vary in size (sometimes being as large as a thaler or even as the palm of the hand), and extend in depth through the corium. They are covered with a brownish-red or blackish tough scab, on the removal or dropping off of which there appears sometimes a foul, ulcerated surface covered with shreds of tissue stained with blood, sometimes a spongy and easily bleeding surface of granulations; in both cases the ulcerated surface secretes a considerable quantity of thin, sanguinolent fluid, often of an ichorous character, and then of highly offensive odor. These ulcers are, moreover, generally surrounded by a broad halo of a dirty violet color; they show little tendency to cicatrize; on the contrary, they are apt to spread both in extent and in depth. In the latter case the ulcerative process may involve some of the larger vessels of the skin, and so give rise to copious and even fatal hemorrhages.

Apart from this, however, these ulcerations exert a very deleterious influence on the general condition of nutrition by the profuseness of the secretion connected with them. The painfulness of these scorbutic ulcers is, as a rule, not very great; still, it contributes its share to the subjective discomfort of the patients.

We mention, finally, the fact that the above-described changes in the skin (hemorrhages, hemorrhagic inflammations, and ulcerations) may also occur in the immediate surroundings of the *nails*. The latter, then, sometimes show simply an extravasation of blood beneath them; sometimes, however, if an inflammatory or ulcerative process has attacked the root or bed of the nail, they may turn brownish-yellow, die, become loose, and at last be thrown off, either wholly or partially (Paronychia et Onychia scorbutica).

After the gums and the outer skin (the nails included), the scorbutic attack localizes itself most frequently in the subcutaneous and deeper *layers of connective tissue*, as well as in the *muscles* and *intramuscular tissue*. These foci of the disease also appear to be located with special frequency on the lower extremities, and in mild cases are indeed entirely limited to these parts of the body. In the more severe forms of the disease, on the other hand, they are observed not only in greater number, but also of greater extent; they are also found on other regions of the body. The loose tissue near the tendo Achillis and that in the hollow of the knee, and further the muscles of the calf of the leg, must be mentioned as the chief localities specially chosen by the scorbutic affections of the connective and muscular tissues; besides these, however, the subcutaneous tissue of the posterior surface of the thigh, as well as of the armpits, and, among the muscles, the recti abdominis, the lumbar muscles, and the pectorales majores, are comparatively often attacked. Moreover, in what has just been said, it is by no means intended to convey the impression that other layers of the connective tissue of the body, or other portions of its muscular tissue, may not now and then be found affected by scorbutic processes. Now, in regard to the outward form of the affections of the connective tissue, these present themselves as swellings, which are at first soft, but later usually become as hard as

a board. The limits of these swellings are in some cases sharply defined, in others less so; the skin over them is not movable, and is variously colored, according to the mode of origin (compare what follows), the time of duration, and the deeper or more superficial site of the focus. The induration may, under circumstances favorable to its development, become very extensive, so that, for instance, at times a considerable portion of a limb (the whole calf of the leg, more than half the thigh, etc.) will be affected by it, and more or less swelled. The manner of origin is not always the same, since these foci are sometimes developed acutely, and then, for the most part, with pains and fever; sometimes gradually, and in this case usually without pain and without fever. If the mode of development be an acute one, there will be noticed, as a rule, on the painful part, which is beginning to become indurated, a very vivid redness of the skin which covers it; this is, moreover, hot to the touch, swelled, and shining. After a few days, the redness, swelling, and painfulness having in the meantime diminished, the skin assumes a brownish tinge, and the epidermis begins to scale off, the latter process being usually repeated several times. Finally, a discoloration, which is apt to last a considerable time, marks outwardly the site of the recent or even still active subcutaneous focus of disease. In other cases, where the infiltration of the subcutaneous connective tissue has taken place in an acute manner, the superjacent skin undergoes a livid discoloration, grows thinner and thinner, and finally ruptures. From the ulcerated opening thus formed, large quantities of bloody matter, mixed with shreds and sometimes gangrenous masses, are then usually discharged, and a foul ulcer remains, offering in its further course the above-described characteristics of scorbutic ulcerations of the skin. If, on the other hand, the process takes place more slowly, without either pain or fever, the hyperæmic redness and the swelling of the skin covering the part will be absent; there will also be no subsequent scaling off and brownish discoloration of the same. On the surface of this swelling, which at first is soft, but subsequently becomes hard, there is merely to be perceived a bluish, greenish, or slightly yellowish tinge, according to the more superficial or deeper site of the

focus. The functions of the neighboring parts, especially the muscles and joints, is naturally very seriously affected by these indurations and tumors of the connective tissue, and, as the usual site of these foci is on the extremities, the power to use the latter, even in those cases in which no serious pathological lesions have occurred in the muscles themselves or in the capsules of the joints, is often materially diminished. It is not a rare occurrence, however, in scurvy, for the muscles of the extremities to be the seat of localized inflammatory processes, which may develop either at the same time with the subcutaneous connective tissue foci described above, and as a direct extension of the latter process, or even quite independently. In the former case it is not possible to recognize the existing affection of the muscles by any special clinical signs observable during the patient's lifetime, nor indeed in any other way than by an autopsy. In the latter case, on the other hand—that is, if it arise independently—the localized disease of the muscle is characterized by the presence of a hard mass, which is more or less sharply defined, sometimes painful, sometimes indolent, but upon which the skin, whose color has undergone no change, is perfectly movable. For the rest, the circumscribed scorbutic affections of the muscles show a great analogy with the similar affections of the connective tissue in the following particulars: they occur at one time as acute processes with fever, at another as subacute or chronic without fever; they are, moreover, naturally accompanied by a decided impairment of the functions of the muscle attacked. The pathological processes and histological changes, which lie at the foundation of the scorbutic affections of the connective and muscular tissues, will be more thoroughly considered farther on; we will, therefore, here only remark in passing that in both these tissues we have to do in part with simple hemorrhagic infiltrations of non-inflammatory nature, in part with hemorrhagic inflammations.

In our description, thus far, we have in general portrayed those features of scurvy which are observed in the greatest number of cases, the mild as well as the severe ones, and which might fairly be considered as the principal characteristics of the disorder, either in its partially developed or in its fully devel-

oped form. In many cases of scurvy either recovery takes place, or the disease terminates fatally, under manifestations of increasing general weakness, without the development of any further local symptoms on any part of the body. As we shall describe farther on the changes which are observed at the autopsy in those cases that end fatally, it is plainly our best course at present to describe next in order, as briefly as possible, the retrograde changes that take place in those local manifestations of the disease (in the gums and teeth, skin, connective tissue, and muscles), which have already been referred to. In these cases, some of which may be even quite severe, the recovery may be either complete or incomplete.

In cases where the affection of the gums has been intense, but yet not of a diphtheritic character nor associated with ichorous disintegration of the mucous membrane, the swelling and redness, under appropriate treatment, may gradually disappear, and in the course of time the parts may return to their natural condition, the edges of the gums becoming again adherent to the teeth. This return to the natural condition, however, requires many weeks, and often months. Again, the restoration may be incomplete ; a hyperplasia is very apt to take place during the stage of convalescence, in the still red and swelled gums, as a result of which they generally remain thickened and indurated during the remainder of the patient's life. These permanently swelled gums, however, do not usually cause the patient any really serious annoyance. Diphtheritis of the mucous membrane which surrounds the teeth, and, still more, fully developed diffuse ichorous degeneration of the same, leads directly to more or less extensive losses of substance of the mucous membrane, which, in favorable cases, are gradually filled up later by the formation of granulations and cicatricial tissue, and may at length be entirely healed. In such cases the teeth may escape damage altogether, or some of them may fall out. Among the cutaneous processes, the petechiæ, ecchymoses and vibices gradually disappear within a few weeks. The scorbutic ulcers of the skin, on the other hand, take the following course : the granulations, which at first are flaccid and bleed easily, become firmer as soon as the patient's general condition improves ; the secre-

tion, moreover, loses its thin, sanguinolent character, and becomes more and more like good ordinary pus; finally, after a certain length of time, the loss of substance is made good by the formation of a brownish-red, dark-colored cicatrix. The indurations of the connective tissue, even where the swelling was very extensive and hard, may in favorable cases gradually grow softer and disappear; yet frequently the last remains of these indurations only disappear after the patient is far advanced towards recovery, and when his general condition leaves nothing to be wished for. In other cases there remains for years, or even for life, an abnormal resistance of the parts which were the seat of these indurations—a result which indicates that a hyperplasia of the connective tissue has taken place at the point of previous scorbutic attack. If these firm masses of callous connective tissue are situated upon or in the neighborhood of the fleshy parts of muscles, there results secondary atrophy and lasting functional impairment of these latter; if they are, as is often the case, situated near to joints, they occasion for a long period, or even for life, a so-called false anchylosis—the immobility of the joint being due to the fact that the tendons, which pass close to it, are enveloped by the growth, or that they form adhesions with the bones that compose the articulation. Such stiffness has been seen to remain, after scurvy in the knee-joint, owing to the presence of indurations in the popliteal space; and in the ankle-joint, owing to the presence of indurations near the tendo Achillis.

Among the forms of immobility of the latter joint observed most commonly at the clinique, are those known as pes equinus, pes valgus, and pes varus—the two latter being of less frequent occurrence than the former. Finally, the hemorrhagic foci in the substance of the muscles generally end in gradual resorption; more rarely there remains (in consequence of an abnormal growth of connective tissue and the formation of a cicatricial callosity) a hardness in the muscle attacked, which is, moreover, in such cases naturally shortened, and becomes the seat of a lasting, more or less pronounced, contracture.

In contrast to the forms of scorbutic disease which have been thus far described, and in which the disease, although severe and sometimes even fatal in character, yet remains limited in

its local manifestations to the parts of the body already mentioned (gums, skin, connective tissue, muscles), there are other forms which are to be looked upon as more severe than the foregoing in this one respect, viz., that the localizations are more varied in character, and especially that they involve to a greater or less extent other regions, organs and tissues of the body than those already named. It may be well at this point to remind the reader that if at the bedside we are apt to find the type of a disease somewhat different from that which is pictured in the text-books, this is especially true of all the different forms of scorbutic disease. In our further consideration of scurvy, therefore, it will be impossible for us to give a comprehensive description of the general course of this affection in its more unusual forms; we must simply limit ourselves to a short enumeration of those parts, organs and tissues in which changes of a distinctively scorbutic character have been observed.

The mucous membrane of the nasal cavities is not unfrequently the seat, in severe cases of scurvy, of serious and dangerous epistaxis, which occurs at times spontaneously,—more often, perhaps, on too violently blowing the nose. These attacks of *bleeding at the nose*, which for the most part cannot be successfully combated without plugging the nasal passages, are considered, and have been long considered, as a very ominous symptom,[1] owing to the exhaustion which they occasion. Profuse *hemorrhages from the stomach* are sometimes observed; they appear under the form of a more or less abundant hæmatemesis, which may at times be ushered in by a very marked sense of oppression in the region of the heart (Duchek).

Hemorrhages from the bowels and copious bloody stools occur more frequently; they are very apt to follow the administration of the active purgatives (compare above), although in other cases they result from a dysentery which, having existed previously, has been modified by the scurvy (compare Special Symptomatology and Complications). These bloody

[1] Compare the passage already mentioned in *Joinville's* Histoire de St. Louis, which speaks of the epidemic of scurvy in 1249, in the army of St. Louis of France: "le signe de la mort était tel, que là, où le nez saignoit, il falloit mourir."

dejections often lead, if very abundant, to rapid exhaustion of the patient, and to death in the course of a very few days; at times they continue somewhat longer, and perhaps even for several weeks in succession the patient may pass per anum, several times daily, sanguinolent masses of a most putrid odor.

Hæmaturia also sometimes occurs in severe cases of scurvy. On the other hand, *hemorrhages from the respiratory organs* are of rare occurrence, and are for the most part only observed in the case of those who are already affected with incipient phthisis, and are consequently already predisposed to hæmoptysis; or in cases where the scurvy becomes complicated by a pneumonia, hemorrhagic infarctions, or gangrene of the lungs. In general, all these hemorrhagic accidents, which occur in the course of an attack of scurvy in the various canals and open cavities of the body, contribute in a very great degree to aggravate the patient's general condition; they are to be considered, therefore, under all circumstances, as very dangerous symptoms.

Of an equally serious nature are the localizations in the *serous membranes*, especially the *pericardium* and *pleura*. These local affections, which are not of rare occurrence in the more severe forms of scurvy, are developed often in a wonderfully short space of time; they are ushered in by fever, and consist of *inflammatory effusions of an hemorrhagic character* (pericarditis, or pleuritis exsudatoria sanguinolenta sive scorbutica), which are clinically marked by the well-known physical signs of pericarditic or pleuritic exudations, and which by their quantity occasion, as a rule, great hinderance to the functions of the heart or lungs, as the case may be. These effusions in severe cases often hasten the end where patients are lying already in a state of complete prostration; in other cases, too, they lead quite directly, of themselves, to death, breaking in suddenly upon the patient, who had up to this time been in a fair general condition, and by their violence and rapid development very shortly endangering life. Of the greatest interest, on the other hand, is the fact noticed by a few observers (F. v. Niemeyer), that even very abundant and suddenly occurring effusions into the thoracic or pericardial cavity, in the case of scorbutic patients, may sometimes be absorbed with almost

equal promptness, if a timely and energetic treatment prove successful in improving the general condition.

Affections of the bones, cartilages, and articulations are among the peculiar complications sometimes observed in the more severe forms of scurvy. The periosteum of the long, hollow bones of the extremities is most often affected, especially that of the tibia on its anterior surface; further, the periosteum of the ribs, of the scapula, of the inferior maxillary, as well as of the palatine process of the superior maxillary bone. These affections of the periosteum, which are generally circumscribed in character, occur relatively often as the result of some mechanical injury (a blow, concussion, etc.) that has befallen the bones; they also sometimes occur without any apparent cause. On the surface of the bones above-named, as well as sometimes on other bones of the skeleton, there are formed painful swellings of varying size and of a certain degree of hardness, which owe their origin to simple hemorrhages or to inflammatory hemorrhagic effusions under the periosteum (periostitis scorbutica), and which, even in favorable cases, are usually reabsorbed only very tardily. The bone itself usually remains intact so long as these swellings of the periosteum do not exceed a certain size, and provided the general condition is early improved; in unfavorable cases, however, and especially if the periosteum be separated from the bone throughout a considerable extent, partial necrosis of this latter, with subsequent exfoliation and expulsion of the dead portions, is very apt to follow. In other cases, again, the epiphyses of the bones become swelled and painful, and at a later stage the cartilage may become partially or even wholly separated from the ends of the bones—a process which has been especially observed on the ribs, sometimes even affecting several of these bones at once. In such cases there is formed, on one or on several ribs, a swelling of the anterior extremity, painful especially on pressure or on the movements of respiration; later there will be developed an angular bend at the point of junction of the rib with the costal cartilage; still later, abnormal mobility and crepitation at this same point; and finally, complete separation of the cartilage from the rib. After this separation, the anterior extremity

of the rib, deprived of its connection with the sternum and without support, now sinks back, while the detached end of the cartilage appears prominently under the skin. Reunion may afterwards take place by reabsorption of the blood and other fluid matter extravasated between the two parts, but they rarely resume their normal position. As a matter of fact, the patients succumb before this can take place, as the affection in question is usually only developed in extremely severe cases (Duchek). Finally, among the scorbutic affections of the bones must be enumerated the softening of the callus of uniting or long united fractures, described by some authors (Aitken, Pringle, Bell, Leveille, Krebel). This softening is accompanied by swelling and painfulness of the parts involved, and has been observed in a number of very severe cases of scurvy. In regard to the scorbutic affections of the *articulations*, these occur sometimes as independent local affections, sometimes as accompaniments of periarthritic processes going on in the neighboring connective tissue. In both cases we have to do with serous, or much more often with hemorrhagic effusions into the cavities of the joints, the process being characterized by great painfulness and constantly increasing swelling of the joint, by active fever, and by the appearance of fluctuation. These effusions, however, if the general disease takes a favorable turn, may, like the effusions into the serous cavities (compare above), also be quickly reabsorbed; it rarely happens that they lead to actual anchylosis. This arthritis scorbutica, for which, as a rule, no special immediate cause could be assigned in the cases reported, has been observed most often in the knee- and ankle-joints, but also in the hip-joint, shoulder-joint, and in the articulation of the jaw.

As very rare local affections of scurvy are to be considered the isolated cases of *intermeningeal hemorrhage*, which usually ran their course under the form of rapidly fatal apoplexy, but also in some cases led to death with the appearances of gradually augmenting compression of the brain: headache, dullness, and finally stupor. It is still doubtful whether or not hemorrhages occur in the substance of the brain; at all events, the remarkable case described by Opitz might have been pointed to

either as a case of scorbutic hemorrhage into the brain, or as one of an acutely developed hæmatoma of the dura mater which subsequently was reabsorbed, or as one of hemorrhage into the pia mater which remained circumscribed. As the patient recovered, it was not possible to determine which of these three suppositions was the correct one.

In the case of scurvy to which we have just referred, convulsions suddenly occurred, followed by loss of consciousness, and hemiplegia of the (left) side of the face and body. Twenty-four hours later the sensorium had become clear again, and the paralysis had disappeared. A moderate degree of headache persisted still for some time, and there was also a slight hyperæsthesia of the affected upper extremity, which lasted about two weeks; later these symptoms also disappeared, and finally the patient entirely recovered from his scorbutic attack.

Finally, among the scorbutic local affections which are not of such very rare occurrence, should be mentioned the affections of the *eye* and its *accessory organs*. Thus, there is sometimes developed, in mild as well as in severe cases of scurvy, an inflammatory process in the conjunctiva of the bulb, as well as of the eyelids (conjunctivitis et blepharitis scorbutica),—a form of conjunctivitis which shows, besides the usual manifestations of this affection (redness, swelling, and increased secretion), those characteristics which stamp it as being scorbutic in its nature. Thus, for example, at an early date, more or less extensive extravasations of blood are pretty sure to make their appearance under the conjunctiva, raising the latter up in many places and causing it to protrude in the form of little sacks filled with blood, which may be sufficiently numerous to cover the whole anterior surface of the eye. In cases which pursue a favorable course, there follows later a gradual reabsorption of the extravasated blood, with disappearance of the inflammatory symptoms. At other times, in addition to the conjunctivitis—or even independently of this—hemorrhages take place into the anterior chamber of the eye, and these often seem to be dependent upon an inflammatory affection of the iris (iritis scorbutica). This latter affection may entirely disappear, or may lead to an abnormal attachment of the iris to the anterior surface of the capsule of the lens. The extravasated blood is either quickly and entirely reabsorbed, or portions of the same remain for a considerable time

in the form of brownish-red spots on the surface of the lens, interfering more or less with the power of sight. The occurrence of hemorrhagic chorioiditis has also been asserted; and finally, sometimes, in very severe cases, which so far have always ended fatally, there arises, in the course of a fully developed general cachexia, a panophthalmitis (generally double), in the course of which the cornea becomes rapidly opaque, and may even undergo ulceration, as a final result of which the eye is completely destroyed (G. v. S. Himmelstiern). We shall not here go into further details in regard to these quite numerous affections of the eye which are observed in the course of scurvy; for further particulars regarding these, we refer our readers to the works of Thielmann[1] and Krebel,[2] as well as to the text-books of ophthalmology.

To close our general examination of the course and manifestations of scurvy, we shall still mention some pathological facts, which, indeed, do not possess that specific clinical character that appertains to the local symptoms hitherto considered, but which nevertheless may prove of value by leading to a clearer understanding of the nature of the disease. Among these facts may be mentioned: 1. The frequent occurrence of enlargement of the spleen during the later stages of the more severe cases of scurvy, —an enlargement which has been verified during life (and also on post-mortem examination) independently of any malarious affection; then 2. The frequent occurrence of *albuminuria* in the more intense cases of scurvy of every sort. Where autopsies were subsequently made, no advanced or even clearly developed affection of the kidneys was by any means found always to correspond with the existence of this latter symptom; these organs, on the contrary, were not seldom found apparently intact (Opitz, Duchek, and others). Interesting, but in a theoretical point of view perhaps somewhat overestimated (comp. what follows), are further, 3. The statements of Duchek in regard to the *comparative quantities of the various normal elements of the urine* in the case of a number of scurvy patients carefully examined by him for this purpose. It was found, for example,

[1] Die scorbutische Augenentzündung. Med. Zeit. Russl. 1844. Nr. 1 u. 2.

[2] L. c. S. 179–186.

that with the increase of intensity of the scorbutic disorder in general, not only was there *a decrease of the amount of urine* secreted, but also a *decrease of all the solid elements of the urine* with the exception of the potassa (and of the phosphoric acid); while *vice versâ*, as improvement occurred in the scorbutic symptoms, the urine again increased in quantity, and at the same time the normal quantitative relations between the solid elements of the urine were restored. We shall return again to this matter farther on, and only give here very summarily the evaluations stated by Duchek:

Duchek's[1] examinations were conducted in the cases of six scurvy patients. In the first period of the disease the quantity of urine passed in twenty-four hours fell to 1500–1200 cubic centimetres—in one particularly severe case as low as 830 cubic centimetres; further, the specific gravity fell to 1015–1009. Specially noticeable was the want of proportion between the amounts of potassa and of soda secreted in the first period, since, while the former remained almost the same as under normal conditions, and in three cases even increased somewhat, the latter decreased so much and so quickly that, in place of the normal proportion of 1 : 12 between the two alkalies (potassa and soda), the proportion was now on an average 1 : 1.9. On the other hand, during the second period of the disease the secretion of potassa experienced a slight absolute lessening.

Finally, it has again and again been mentioned in the course of this article that many local affections of scurvy may run their course with *fever*. In opposition, however, to these results of observation, it must be remarked that the temperature of the body is not influenced specially by general scurvy, at least not to the extent which would justify us in designating the increase as fever. On the contrary, when the temperature during scurvy reached a fever point—and this occurred in fact in almost all severe forms of the disease at some time or other—then there always existed at the same time such local processes (of an inflammatory nature) as would in all probability have induced fever even in non-scorbutic patients.

Post-mortem Appearances.

The bodies of those who have died of scurvy show, as a rule, slight rigidity, early decomposition, and extensive *cadaveric*

[1] Oestr. Jahrbücher. 1861. Bd. XVII. S. 39.

spots; they appear, moreover, emaciated in varying degree (according to the duration of the disease), though at the same time there is often dropsical swelling, especially of the lower limbs. The skin is usually of a dirty grayish-yellow color, dry and leathery to the touch, and covered with abundant epidermis scales. On the trunk and extremities (almost never on the face) are to be seen, varying in number, size, form, and topographical distribution, the hemorrhagic eruptions of the skin, already described on a previous page. A more careful microscopical examination of the parts so affected shows that, in the case of the smaller (petechial) forms of purpuric eruption, the extravasation of blood almost always proceeds from the very close and fine network of capillaries surrounding the hair-follicles, since the extravasated red corpuscles of the blood are only found deposited in the meshes of this network and in its immediate neighborhood. The larger hemorrhagic eruptions (ecchymoses, vibices) are naturally occasioned by more extensive extravasations of blood, which will be found at one time to have emanated from the more superficial, at another from the deeper capillary network of the corium. The hemorrhagic foci existing in the more homogeneous and compact upper layer of the corium (pars papillaris corii) are, as a rule, less spread out in surface than those which are more deeply situated in the laxer tissues of the pars reticularis corii; but the former are almost always complicated by the entrance of blood into the deeper layers of the epidermis, especially into the so-called rete Malpighi. Microscopical examination teaches that it is not only in the case of vesicular and bullous eruptions (purpura vesiculosa—pemphigus scorbuticus) that the blood extravasated from the superficial capillaries of the skin becomes collected on the surface of the papillæ, but that the same process, on a much less extensive scale, goes on also in the macular forms of purpura, since in these, too, it will be found that the rete Malpighi has been invaded by the red blood-corpuscles (Opitz). Now, whether the cutaneous hemorrhage has been superficial or deep-seated, we shall find—if, as is usually the case, it is of quite long standing — that only very few of the blood-corpuscles which are deposited in the rete and corium are well preserved, the greater

part of them having begun to disintegrate and to lose their coloring matter in a greater or less degree. It will be found, too, that the neighboring tissues have, as a rule, imbibed this coloring matter, or it has been deposited in separate particles here and there among the tissues in the form of small grains, lumps, or flat pieces of various colors (yellowish-red, brownish, black).—In regard to the coarser anatomical characteristics of scorbutic ulcers of the skin, we refer to what has been already stated by us in the description of the disease; no very accurate histological descriptions of the behavior of the edge of the ulcer, of the granulations, etc., are to be found in the literature of scurvy up to the present time. Those *indurations of the subcutaneous connective tissue*, and of the deeper layers of connective tissue, which have been recognizable by palpation during life, prove at the autopsy to be infiltrations of the tissue by extravasated blood which has coagulated, and the color and condition of which depend upon the recentness of the extravasation. These infiltrations present different characteristics: some are rather firm, some softer in consistency; some are sharply defined, and may then in some cases even be enucleated, while the limits of others are less clearly marked. In the more recent foci there will still be found a dark cherry-red or brownish-red cruor of gelatinous consistency in the midst of a clearly distinguishable network of fibres of connective tissue, which are of a yellowish or reddish hue; on pressure or section a reddish serum may be caused to exude from the clot. In the case of foci of older date, on the other hand, we have yellowish-brown or grayish-yellow, firm and homogeneous deposits of fibrine within which the tissue-elements (fibres of connective tissue) can only be found with difficulty. In still later stages, and in the case of such extravasations as were apparently beginning to be dissipated during life, the still existing fibrinous masses will be found to have again become softer and more friable, yet at the same time more decolorized than before; and the network of connective tissue, which could previously hardly be distinguished, will now be found to be more plainly recognizable and of gelatinous consistency. Finally, if the mass represents a focus of ancient date, which has at the same time retained its hardness, then, on

cutting into it, the knife encounters an almost cartilaginous resistance, and, as a rule, meets with callous masses of connective tissue of a yellowish or brownish color, but no longer any fibrinous clots and sanguinolent infiltration. If extensive callous solidifications of this sort have taken place in the subcutaneous, subfascial, and intermediate connective tissue, then the muscles lying beneath or imbedded in this tissue are seen to be atrophied; their tendons are often abnormally attached to the bones, or are, as it were, actually walled up in the fibrous tissue, and the joints to which they belong are by this means often brought into a condition of so-called false anchylosis. Thus are to be explained, for instance, those displacements of the osseous parts composing the ankle-joint which are known under the names of pes equinus, pes valgus, and pes varus (comp. Description of the Disease). In regard to the more recent foci in the *muscles*, it must be said that the anatomical changes which characterize these are similar in every respect to those of the more recent foci in the connective tissue, since here, too, we have to do with infiltrations of extravasated blood into the fleshy part of the muscles. That portion of the muscle which is thus impregnated with clotted blood appears of a dark cherry-red or even blackish color; it is, moreover, somewhat hard, yet much less firm than the muscular tissue which remains in its normal state, and may for this reason be easily crushed by careless handling. On the other hand, in the case of muscular foci of older date and which have not become resolved, we find, as in the case of lasting indurations of the connective tissue, on section of the shortened and much atrophied muscle, at the point where induration could be felt, scarcely anything besides callous cicatricial tissue.

Much less uniformly do we find, at the post-mortem examination of those who have died of scurvy, lesions of the *articulations* and *bones*, in addition to those which have been described of the skin, the connective tissue, and the muscles. Sometimes, however, on opening one or another articulation which has been found to be swelled, there flows out a serous or a sanguinolent fluid from the opened cavity, whose walls (cartilage, capsular membrane) may then on examination prove to be in a normal condition, or may appear more or less severely affected. The latter is

very likely to be the case where the effusion is hemorrhagic in character, in which event there will pretty often also be found partial ulcerations of the capsule of the articulation, effusion of blood between the cartilage and the epiphysis of the bone, separation of the cartilage, and pulpy softening of the ends of the bone under the same. The following may also be mentioned as among the lesions which are sometimes observed in the bones: collections of clots of blood, or of sanguinolent jelly-like substance between the periosteum and bone, separating the periosteum from the bone, and complicated for the most part by partial necrosis and softening of the bone, and frequently, too, by ulceration and degeneration of the periosteum itself; further, detachment of the tendinous insertions of the muscles from the bone thus altered and diseased; finally, extravasations within the bone, especially in the midst of the spongy tissue, which is at such points almost always more or less softened, and has been at times found to form a deliquescent, gelatinous mass.

Now, in regard to the remaining parts, the *mucous membrane of the mouth*, in the first place, must be again shortly considered here. As a rule, in cases of scurvy which have terminated fatally, the gums of the cadaver show still more plainly and visibly those phenomena of extreme swelling, of diphtheritic sloughing, or of ulceration, which had been observed during life. Only the redness is less pronounced than during life, since this is in part owing to an active congestion of the vessels of the mucous membrane, which naturally disappears at death; while, on the other hand, the condition of hemorrhagic infiltration of the mucous membrane, and the lividity of the same caused by this, is particularly distinct, both to the naked eye and on microscopical examination, owing to this same (post-mortem) absence of congestion. A microscopic examination shows, indeed, that the whole of the diseased tissue is more or less thickly studded with the red corpuscles of extravasated blood. If the case under examination be one of older date, which has run a long course, the thickened gums may be found compact, firm, and nodular; a careful examination shows that this departure from the usual state of things is occasioned by a new formation of connective tissue, which has taken place in the gums

after they have been infiltrated with blood. The rest of the mucous membrane of the mouth shows in scurvy, on the cadaver as well as during life, but slight alterations; its color is for the most part somewhat bluish, and it is only rarely that it presents more serious lesions in the form of hemorrhagic infiltrations or ulcerations with loss of substance.

Among the *organs of the thorax*, it is the *pericardium* which is most frequently attacked, and next to that the *pleura*. In one or more (sometimes even all three at once) of these serous sacks, considerable effusions of a fluid, either clearly sanguine or at least stained with blood, will often be found. The quantity of this fluid, as we have just remarked, is frequently very great, and may, for instance, in the pericardium alone, amount to several pounds. In addition, however, to these exudations, evidences of inflammation are also pretty constantly found in the serous membranes, namely, increased injection of the vessels, fibrinous deposits, and finally hemorrhagic spots, which owe their origin to an extravasation of blood into the tissue itself of the pericardium and pleura. Ecchymoses of this sort are seen more especially on the epicardium as well as on the pleuræ pulmonales; extravasations of greater or less extent also occur under the serous coats, in which case the extravasated blood is deposited in the form of hemorrhagic foci directly upon the surface of the heart and of the lungs. The *heart* is usually flaccid, its muscular fibres pale, and probably in prolonged cases also affected with fatty degeneration. Hemorrhages have been mentioned as at times occurring in the muscular tissue of the heart, likewise occasionally evidences of endocarditis valvularis. The *tissue of the lungs* is for the most part the seat of a bloody œdema, which is very frequently accompanied by hypostases in the form of catarrhal-croupous solidifications of the tissue of the lungs in their inferior and posterior portions, on both sides. Somewhat less frequent are the firmer hepatizations in other localities; still, even extensive croupous pneumonia of one or the other lung has been observed in some cases (as a simple complicating process). Finally, in quite a number of cases the lungs contained more or less numerous hemorrhagic infarctions—in a few, even gangrenous foci of greater or less extent. The *mucous*

membrane of the bronchi almost always exhibits extensive and numerous ecchymoses on an otherwise pale surface, and is usually covered with abundant bloody mucus. The *mucous membrane of the larynx* is found in a similar condition, and, moreover, shows at times œdema in a very marked degree.

There is also found at times in the *abdominal cavity*, although much less often than in the thoracic cavity, an hemorrhagic effusion accompanied by fibrinous secretions and deposits on the parietal and visceral serous surfaces, and numerous ecchymoses. On the *mucous membrane of the stomach and small intestine* are seen hemorrhagic spots and erosions, and at times more profound losses of substance, penetrating even to the muscular coat and showing villous edges infiltrated with blood (Opitz); blood, either clotted or in a half fluid state, is also frequently mingled with the contents of these portions of the bowels. The *mucous membrane of the large intestine* generally presents very marked lesions in those cases in which frequent bloody stools occurred during life (Samson-Himmelstiern, Cejka, Duchek). The mucous membrane appears swelled, is studded with very numerous hemorrhagic infiltrations, and is remarkably tender (which explains why it bleeds so very easily); in some places a brownish-red, pulpy mass, at times quite considerable, may be wiped off from the surface of the mucous membrane, and the subjacent tissue is then found to be destroyed or quite filled with blood and softened. In other cases there is extensive follicular ulceration (Cejka), generally accompanied by an hemorrhagic infiltration of the edges of each small, roundish loss of substance. The contents of the large intestine are, like those of the stomach and small intestine, for the most part mingled with blood. The *liver* shows no pathological peculiarities other than hemorrhagic spots on its surface. The *spleen* is sometimes of normal size, much oftener, however, appreciably enlarged, and in this case contains more blood and is of diminished consistency. At times, moreover, there exists in this organ wedge-shaped, hemorrhagic foci. In the *pancreas*, effusions of blood were on various occasions observed by Cejka. The kidneys seem often to have been found in a quite normal condition, even where albuminuria had existed during life (Opitz, Duchek); at other times, however, in cases

where the urine during life had contained large quantities of albumen, the evidences were found of a commencing or even of a well-developed parenchymatous degeneration of these organs (Cejka, Krebel); finally, in a few protracted cases even atrophy of the kidneys was observed (Opitz). Hemorrhagic spots were sometimes observed on the capsule of the kidneys; infarctions too, of various size, have been seen in the cortical substance, less often in the deeper tissues. The *mucous membrane of the pelvis of the kidney, of the ureters, and of the bladder*, was often the seat of ecchymoses as well as of erosions, the contents of the urinary passages being in such cases for the most part tinged with blood. In the general description of the disease we mentioned very briefly the anatomical changes which may occur in scurvy *within the skull* or in the *organs of sight.*

Finally, in a disease like scurvy, which manifests itself by such prominent hemorrhagic symptoms, the *condition of the blood-vessels, especially the capillaries*, as well as that of the *blood* itself, deserves special consideration. But, strange to say, up to the present time no descriptions of any value in regard to the condition of the walls of the capillary vessels are to be found in the literature of scurvy—a fact which of itself would justify the conclusion that at least no positive anatomical changes of a very marked character are uniformly present in these vessels. This presumption, too, is in harmony with the result of the examinations of Lasègue and Legroux, who during the epidemic occasioned by the siege of Paris (1871), examined carefully the condition of the capillaries on the bodies of seven patients who had died of scurvy, and could discover nothing abnormal there, beyond very scattered fatty granulations. Now, in regard to the condition of the *blood*, this important question too, like that respecting the state of the capillary walls, has up to the present time given rise much more to theoretical speculation than to exact observation and examination. We must not, however, be surprised at the small number of analyses of the blood that have been made in this disease; we must remember that in recent times it is only seldom that an opportunity has been offered to take blood from scurvy patients in sufficient quantity and sufficiently pure to serve for examination; and we must also not forget that any

direct attempt to take blood in this disease is attended with danger. Our knowledge of the condition of the blood of scurvy patients is, therefore, limited principally to the very rough results offered by an inspection of the blood of the cadaver in fatal cases, and to the results of a small number of microscopic and chemical analyses made only with partial accuracy on blood taken by the lancet or by cups during life.

Autopsies showed that, where the disease had lasted but a short time, the blood found in the cavities of the heart and of the larger vessels was, as a rule, of dark color; moreover, that it was sometimes fluid or only partially clotted, and sometimes firmly coagulated; while, on the other hand, where the duration of the disease had been longer, the blood was rather of a lighter color and in a more fluid state, without, however, an entire absence of firm coagulations of fibrine even in such cases. These results by no means justify the conclusion that these alterations of the blood are in any sense specific, since precisely the same properties are discovered in the blood of the cadaver in innumerable cases of those who have suffered with quite different severe diseases of shorter or of longer duration. Nor has the matter been made really clearer as yet by the results of microscopic and chemical analysis; and absolutely nothing characteristic, hardly even anything constant or positive, can be gleaned from the statements of those investigators who have formerly or even quite recently devoted themselves to this subject. Now, in regard to the *red blood-corpuscles*, the examinations bearing upon this subject showed in the first place no anomaly in the form, that is, no shrinking of the blood-disks, as had been formerly assumed on no other ground than that of certain theoretical ideas (of an increase in the amount of salt contained in the blood of scurvy patients, and of a loss of water from the corpuscles occasioned by this) (J. Vogel). In regard to the aggregate number of the red blood-corpuscles, the statements of different authors vary, since some (Opitz) report that they have found the blood still very rich in these bodies in severe forms of scurvy; while others (Becquerel and Rodier, Chalvet), on the contrary, report that they have found a noticeable diminution in the num-

ber of the same in the advanced stages of the disease. Just as various, too, are the statements in regard to the amount of iron contained in the blood, which Opitz and Schneider report to be somewhat increased, Duchek to be about normal or slightly diminished, while Becquerel and Rodier, as well as Chalvet, report it to be (corresponding with the numerical decrease of red corpuscles seen by them) considerably decreased. According to Chalvet, too, the amount of *potassa* contained in the blood decreases in a degree corresponding to the diminution in number of the red corpuscles, a statement which has nothing surprising in it under the presupposition of oligocythæmia rubra, since potassa, like iron, is a preponderating element of the red blood-corpuscles only, while under normal conditions it exists in only very minute quantity in the plasma. Garrod, too, thought that he found the blood of a scurvy patient lacking in potassa, in an analysis which he formerly made (unfortunately, in a very imperfect manner), and by the aid of this untrustworthy result sought to give a further positive ground for his theory in regard to the nature and pathogenesis of the disease—a theory to which we have already alluded in the Etiology, and which is in other respects most worthy of attention. But, without further consideration, it must be clear to every one that quite as little useful advance would be made towards the theoretical comprehension of scurvy by the simple proof of a lessening of the potassa, as of the iron, contained in the *blood considered as a whole*, since both these changes (the diminution of iron as well as that of potassa) must be supposed to have taken place in every other oligocythæmia rubra. Now, as these changes undoubtedly take place in the various forms of anæmia, and still more in chlorosis (compare the chapter treating of this in volume XVI.), it is impossible to consider them as really pathognomonic characteristics of the blood of scurvy patients, or to attempt to explain the disease in this way. For the purpose of testing Garrod's theory that the diminution of the amount of potassa is the true and exclusive cause of the constitutional scorbutic affection, it would be far more important and convincing to obtain *comparative estimates of the amount of potassa contained in equal volumes of scorbutic and non-scorbutic red corpuscles*, and to

these might further be added analogous estimates of the amount of potassa contained in other tissues specially rich in potassa (particularly the striated and non-striated muscles). Examinations of this sort have not, at least to our knowledge, been as yet undertaken by any one; we cannot, therefore, here make reference to any such.—In regard to the behavior of the *white blood-corpuscles*, recent statements (Laboulbène) indicate a considerable increase in the number of these bodies in pronounced cases of the disease; in these reports, however, there is wanting anything to prove that the leucocytosis apparent to the microscope was also really absolute in the cases referred to, and the supposition is certainly allowable that the increase in number of the colorless corpuscles formed only an apparent departure from the normal, caused by the decrease in number of the red corpuscles. But even supposing that absolute leucocytosis of the blood regularly existed in scurvy, the proof of this would still offer nothing pathognomonic, since it is well known that this departure from the normal has been of late observed in processes of disease most widely differing in character. Formerly speculation turned with very marked preference to the *fibrine* of the blood, and a decrease in this element was supposed to be the most important, perhaps the only change in the blood of scurvy patients by which especially the hemorrhagic diathesis was to be explained. When careful examinations, however, were really made, they did not by any means regularly prove a decrease of the fibrine; more often it was found to be present in normal quantity, and a few of the earlier as well as more recent analyses have shown even an increase in its amount. Thus, for instance, Becquerel and Rodier, in five scurvy patients examined by them, found the amount of fibrine to vary between 2.2 per cent. and 4.1 per cent.; Opitz and Schneider found it in one case to be 3.4 per cent.; finally, Chalvet, as well as Lasègue and Legroux, found the quantity of fibrine to be about twice as great as it should be in a healthy individual, say 2.0 per cent. From these numerical data we may at least gather so much as this—viz., that the scorbutic manifestations cannot be attributed to a "hypinotic condition" of the blood, and that theories grounded upon this supposed quality find no support in chemistry.

Andral and Gavarret, Becquerel and Rodier, Favre, Schneider, and some others, state that the amount of albumen contained in the blood is diminished; while Chalvet, on the other hand, maintains that it is increased. Authorities also disagree in regard to the salts of the serum of the blood, some holding that there is an increase in the alkalinity of this fluid, others that there is an increase in the amount of chloride of sodium, both of which conditions are held to be the cause of the scorbutic manifestations. For example, while Becquerel and Rodier in particular, as well as Denis and others before them, thought that they had found, in their examinations, an increase in the salts of the blood, especially of the chloride of sodium, to double the normal amount, and attributed to this excess the assumed diminished coagulability of the blood of scurvy patients, Schneider and Opitz were able by their analyses to prove the contrary, viz., a diminution in the amount of salts.—Now, if we take a general survey of the total results of the analyses made of the blood of scurvy patients up to this time, we can hardly avoid a feeling of dissatisfaction. From the various and contradictory statements of different authors we obtain but *one*, and that a decidedly *negative* result—namely, that the condition of the blood of scurvy patients, so far as we understand it at the present time, shows no peculiarities which might not occur as well in other pathological processes.

Special Symptomatology.

Analysis of the Symptoms of the Disease and of the Anatomical Changes.

In this section we will endeavor to illustrate, by a few explanatory remarks, the account of the more important clinical and anatomical data bearing on scurvy, that has been given in the two preceding sections of this chapter. In this way we shall perhaps succeed in attaining a more exact theoretical comprehension of the affection.

Since in the majority of cases the characteristic clinical pic-

ture of scurvy is ushered in by the development of a peculiar *cachexia*, and since this disturbance, which affects the subjective as well as the objective condition of the entire organism, persistently maintains a very conspicuous place among the various local scorbutic phenomena throughout the whole course of the disease, it seems necessary to give it the first place in the special consideration of the symptomatology as well as in the general clinical picture. It really looks in most cases as if all the other local manifestations of scurvy were developed from the already existing or *primordial* cachexia, and especially as if the facility with which the subsequent local processes are evolved in different parts of the body, as well as the intensity of these local processes, stood in a direct ratio to the severity of that general pathological condition!

The *cachexia of scurvy* resembles in many respects that of *anæmia*, particularly in the loss of power in the voluntary muscles, but also in the diminished force of the heart's action, and in the prostration of most of the vegetative functions of the body. The following symptoms may, however, be considered as more especially characteristic of the former, because they are at least not so constant and so marked in simple anæmia, even when it is excessive: rheumatic pains in the muscles—which are almost always present even in the initial period, and which later often attain an excessive degree—and the usually excessive psychical depression, which is also one of the earliest symptoms of the change in the general condition in scurvy, and which, as we have already remarked, cannot be ascribed entirely to the often unfavorable surroundings of the patients. It is, moreover, worthy of remark, that the bodily languor of scorbutic patients very often reaches an unusual degree of intensity even before the occurrence of local symptoms, and that it makes its appearance in general at an earlier period, and with more intensity, in scurvy than in the idiopathic or essential forms of simple anæmia. In a case of fully developed scurvy, the prostration is excessive, and can only be compared according to its intensity with the weakness and exhaustion that are observed in the acute anæmia following great loss of blood, or in the more severe forms of symptomatic anæmia accompanying fever, carcinoma, etc., or perhaps

in progressive pernicious anæmia. At the same time, however, the pallor of the visible parts, especially the mucous surfaces, is far from reaching that degree of intensity in scurvy which we are accustomed to find in simple severe oligocythæmia (or oligochromæmia); it is often even entirely absent when the disease has lasted but a short time, although a very marked disturbance of the general health may already exist and the patients perhaps already feel exceedingly wretched and feeble. Further, the change in the color of those parts that in health are vividly injected (the cheeks, lips, etc.), is especially distinct in the early periods of scurvy, but the parts become livid (cyanotic) rather than pale (anæmic). The tinge of the affected parts resembles more the dull bluish-red observed in patients whose blood contains sufficient colored elements, but in whom hæmatosis (decarbonization) is incomplete in consequence of weakened action of the heart or of some other derangement of the circulation. Direct observations, moreover, seem to show that the blood of scorbutic patients in the earlier stages of the disease is not paler, but is rather of the normal color or even darker than normal blood; that consequently neither the number of the red corpuscles nor the amount of coloring matter contained in them has undergone any positive decrease (Schneider and Opitz); on the other hand, they prove that the circulation is affected and rendered slower at a very early period, as a result of actual adynamia of the heart. Hence, we are finally compelled to assume as necessary that *the weakness of the heart, the muscular debility, and the other manifestations of the scorbutic cachexia, probably owe their origin to something else than an ordinary oligocythæmia.*

When, however, the disease is of long standing, the patient really becomes pale and anæmic to a degree dependent on the duration and severity of the attack, and particularly on the number and copiousness of the hemorrhages, the height of the fever, etc. In such cases a true anæmia is actually superadded to the scurvy as a complication or a sequel. Moreover, theoretical considerations, which we will discuss more fully farther on, lead us to believe that, as the scorbutic cachexia increases in intensity, the reproduction of the red blood-corpuscles is gradually more and more interfered with, and that in the later

stages of the disease an oligocythæmia is developed, which is not entirely consequent upon loss of blood, fever, etc., but is due to an actual interference with the development of the blood-tissue. While asserting, however, this well-grounded opinion, that oligocythæmia occurs as an accidental change in the constitution of the blood, in the later stages of many severe cases of scurvy, we do not mean to insist less on the above-mentioned, and, as we think, equally well-grounded opinion, that the cachexia of scurvy is in itself and originally not an oligocythæmia (or oligochromæmia), nor an anæmia at all, *but a special and independent constitutional affection.* In addition to the peculiarities (rheumatic pains, psychical depression) already spoken of, we may, therefore, in accordance with the details given above, mention explicitly as a prominent characteristic of this pathological species, a very severe functional derangement of the motor apparatus (the heart and the voluntary muscles), which must not be ascribed, as in anæmia, to a want of hæmoglobine in the blood. As the cachexia of scurvy progresses, however, it is characterized, as a special form of constitutional disorder, particularly by *its local developments*, which are *peculiar* in their nature, and are not met with in the same form in any other general disorder. Let us now briefly consider what the clinical picture and the anatomical lesions have taught us in regard to each of these local processes: as the *scorbutic affection of the gums* is the most frequent, and generally also the earliest local symptom of scurvy, we will consider it first, and study more closely its nature and mode of origin. The histological changes in, and clinical appearances of the gums, even in the slighter forms of the affection, show that we have to deal with a decidedly *inflammatory* process, which begins with hyperæmia and extravasation of the fluid elements of the blood, and leads to redness and painful swelling of the parts affected. The peculiarities which distinguish this stomatitis marginalis from other inflammations of the mucous membrane of the mouth, are the great tendency of the diseased mucosa to bleed upon pressure, touch, etc., and the fact that the affected part is not only hyperæmic and œdematous, but is also at the same time hemorrhagically infiltrated. The question whether

this extravasation of red blood-corpuscles into the tissue of the mucous membrane owes its origin, like the traumatic bleeding of the gums, to a rhexis of the capillaries, or, in addition to this, also to a simple diapedesis through the uninjured walls of the capillaries, must remain in abeyance, since this special point, which is without any great importance for the understanding of the process, has not yet been cleared up. In general, however, we may deduce from the symptoms which exist the positive conclusion that *the character of scorbutic stomatitis is hemorrhagic*, which indicates a *diseased condition* (abnormal fragility, combined perhaps with abnormal permeability) *of the capillaries.*

It is true that in the more severe cases of scurvy the inflammation of the gums not unfrequently takes on a diphtheritic character or leads to diffuse ulceration of the affected mucous surface, but these exacerbations of the inflammatory process are not specially characteristic of scorbutus. It is well known that similar destructive processes are by no means rare in connection with intense inflammations of the mucous membrane of the mouth of entirely different origin (we may refer, for instance, to the more severe forms of stomatitis mercurialis). It would be just as incorrect to attribute exceptional importance to the hyperplasia of the connective tissue, which sometimes gradually takes place in the inflamed gums, and subsequently leads to permanent thickening and induration of the same, since it is likewise a well-known fact that a new formation of connective tissue very frequently appears as a late link in the chain of the elementary processes of inflammation when this has continued for a long time and is mild in form. It only remains for us, therefore, to consider briefly two questions in regard to the scorbutic affection of the gums—two questions which are, however, from their nature, of great importance. These relate, 1st, *to the reason why this particular part of the body is so frequently and so early affected; and* 2d, *to the connection between the hemorrhage and the inflammation* in this peculiar pathological process. In regard to the *first* point, the other local symptoms in scurvy demonstrate sufficiently that neither the predisposition to hemorrhage nor that to inflammation is limited in this disease

to the gums, but that, on the contrary, all possible parts and tissues participate in it. Further, a number of isolated observations prove not only that the affection of the gums is not always the first local manifestation of the disease, but also that it may even be absent during the entire course of the disease. Finally, these observations teach in particular that the *anomalous* primary local manifestations of scurvy occur especially on such parts of the body as have been in some way (mechanically, chemically, etc.) *injured*, and that, on the other hand, the development of the affection of the gums seems to be dependent upon the existence of teeth in the jaws, and therefore upon the act of chewing. All these circumstances taken together render it at least very probable *that the inflammatory and hemorrhagic affection of the gums occurs usually so early and so constantly in scurvy simply because they are, considering the tenderness of their histological structure, exposed to such various and severe mechanical, chemical, and thermic irritations* (in seizing and masticating hard alimentary substances, in the ingestion of highly seasoned articles of food, hot drinks, etc.).

In considering the second point (connection between the hemorrhage and the inflammation), we must recall first the later local manifestations of scurvy, which were described in the section on General Symptomatology. They prove that extravasations occur with remarkable facility in scorbutic patients without connection with any previously existing inflammation, but as direct results of injury of any kind; they occur then at the very point injured. *This behavior allows us to conclude that there is an alteration in the walls of the capillaries, entirely independent of inflammation*, and which may be loosely characterized as a *diminution in their power of resistance*. On the other hand, it is clear that the inflammatory hyperæmia, which causes dilatation of the capillaries, may, where the resistance of these is insufficient, lead to a direct extravasation of blood by rupture and by diapedesis, precisely in the same way that this is brought about by any lesion due to external causes. It is therefore allowable to regard the bleeding of the gums in scurvy, whether it be superficial or interstitial, as the effect of

the combined action of external irritants and of inflammatory hyperæmia, and to explain it by both these factors acting together. On the other hand, however, it cannot be denied that an inflammation is now and then primarily excited, or an already existing inflammatory process aggravated, by the occurrence of interstitial bleeding, the blood extravasated into the interstices of the tissue acting as an inflammatory irritant. Finally, we must also bear in mind that, *vice versa*, any inflammatory alteration in the tissue of vascular parts, quite independently of the accompanying hyperæmia, influences in a very direct manner the power of resistance of the capillary tract affected, and thus of itself predisposes to hemorrhages.

We have intentionally devoted considerable space to the consideration of the scorbutic affection of the mouth, not only because it seems to us to be particularly important on account of its frequency and its early development, but also because it is, in our opinion, specially adapted to facilitate the comprehension of the genesis of *other* scorbutic local affections. If we consider next the scorbutic processes in the *outer skin*, in the *connective tissue*, and in the *muscles*, which we have already described, we find that in them, too, the hemorrhagic nature of the disturbance is exquisitely marked. These affections of the skin, connective tissue, and muscles are at times purely hemorrhagic in character, *i. e.*, hemorrhages often take place in these parts during the course of the disease, either spontaneously or after slight injuries, although no other gross lesions, and particularly no signs of inflammation, are present. In this way are produced, for instance, simple petechiæ, ecchymoses, and vibices of the skin, and also those hemorrhagic infiltrations of the subcutaneous connective tissue and of the muscles which are developed without inflammatory redness of the skin covering the part, without fever and without much pain. At other times, however, the hemorrhages accompany and are symptomatic of inflammatory processes, *ex. gr.*, in purpura papulosa, pemphigus, and rupia scorbutica, and also in those foci in the connective tissue and muscles which are developed more acutely, with pain, redness of the skin, and fever. Finally, in still other cases the clinical symptoms seem to indicate that the

hemorrhage is the primary process, to which the inflammation is secondary, being excited by the interstitial effusion of blood. In short it is, on the whole, easy to trace a pretty complete analogy between the pathological process in these parts and the scorbutic alterations of the gums—an analogy, moreover, which continues throughout the entire course and in the terminations of the morbid processes. For, in the skin, the connective tissue, and the muscles also, under favorable circumstances, reabsorption of the extravasated blood and resolution of the inflammation can take place, and the process finally terminate in complete recovery in loco. Under unfavorable circumstances, on the contrary, the inflammation may take on a more malignant character, and lead to destruction of the tissue, or finally, it may gradually terminate in hyperplasia of connective tissue and leave behind a permanent induration (callosity, cicatrice).

The case is exactly the same with the *affections of the bones and of the periosteum*, which, however, are more rare, as well as with the *affections of the joints*, which sometimes occur in scurvy. The clinical manifestations during life, and more especially the lesions found after death, prove beyond question, that in the scorbutic affections of these parts we have also to deal with hemorrhages, or relatively still oftener with inflammations of a hemorrhagic character. These alterations, in their further development, do not in general present, either clinically or anatomically, any peculiarities that are specially characteristic of scurvy. Like the local scorbutic affections, which have been already investigated, their terminations are for the most part the natural, and indeed, the necessary consequences of the morbid processes that have been set up, and of the abnormal conditions of nutrition in the parts affected, occasioned by these processes.

For instance, no one would be surprised to find that a portion of bone situated under a periosteal extravasation or hemorrhagic exudation in a scorbutic patient has become necrosed, since under all circumstances this is the usual fate of bone when deprived of its nourishing periosteum. For the same reason, there is nothing in itself remarkable or peculiar to scurvy in the necrosis of the cartilage when it has been detached by hemorrhage from the bony epiphysis, or in the ulceration of the capsule of the joint, that is occasionally observed in intense scorbutic arthritis.

With regard to the *scorbutic affections of other mucous membranes* than that covering the gums, the *epistaxis* constitutes a simple hemorrhage, from the abnormally tender capillaries of the nasal mucous membrane, excited for the most part by the mechanical irritation of blowing the nose. The genesis of the hæmaturia and of the *hemorrhages from the stomach and intestines* is less clear. As a rule, however, they are not preceded by inflammation, but rather present anatomically the characteristics of simple hemorrhagic processes. The case is different with the *hemorrhages from the large intestine;* here the post-mortem examination most frequently reveals, as the cause of the bleeding, a severe inflammatory alteration of the mucous membrane of a dysenteric (diphtheritic-ulcerative) character. The etiological connection of this inflammation with the general scorbutic disorder is probably not the same in every individual case.

In the first place, different authors (comp. Etiology) have of late years drawn attention to the frequent coexistence of epidemics of scurvy and dysentery, and insisted particularly on the increased predisposition of patients suffering from diarrhœa to the development of scurvy. There can be, therefore, no doubt that the affection of the large intestine existed previously to the development of the scurvy in many of the cases in question; the latter only added to the clinical picture of dysentery certain symptoms specially peculiar to itself, in particular the pronounced hemorrhagic character of the stools, and thus produced the so-called dysenteria scorbutica, or scorbutic modification of the dysenteric process. *Secondly.*—Scorbutic patients may subsequently become affected with dysentery by infection with dysenteric poison. Abundant opportunity for this is often presented in naval expeditions to the tropics, in besieged cities, etc. Here, too, we have to deal with a combination of two different processes, but in an inverted order to the above; and a special clinical type, namely, the hemorrhagic, is impressed on the dysentery by the already existing scorbutic disorder. *Thirdly.*—Even without previous or subsequent infection with the specific poison of dysentery, it seems that a severe hemorrhagic ulcerative process may sometimes be set up in the

mucous membrane of the large intestine in scurvy (Duchek). This process, which is usually exceedingly deleterious in its action, then constitutes an actual localization of the general disease, and corresponds perfectly in its pathological type with the more severe form of affection of the gums observed in so many scorbutic patients. Whether it is the mechanical injury occasioned by hard fæcal masses, or the more chemical irritation of the mucous membrane by undigested and decomposing matters contained in the intestine, or some other noxious influence that constitutes the immediate exciting cause of this *local* scorbutic affection, we are for the present unable to state. It is, indeed, most probable that the direct exciting cause is not the same in every case.

Duchek, although he concurs in general with the opinion advanced by G. v. Samson-Himmelstiern and Cejka, that this affection of the large intestine is in the majority of cases a complication, nevertheless believes that it is also at times merely a localization, and not an independent complication of the scurvy. He repeatedly saw the affection set in in scorbutic patients in the hospital, after the disease had existed for a long time, and terminate fatally by causing frequent intestinal hemorrhages. In these cases there was no reason to suspect a dysenteric infection. He believes that an hemorrhagic infiltration of the mucous membrane of the large intestine, which accompanied the surface bleeding, was probably the cause of the ulcerative destruction.

The *sanguinolent effusions into the pleura* and the *pericardium*, as well as the much less frequent effusions into the *peritoneal cavity*, seem to be almost always the product of an exudative *inflammation* of these serous membranes, which is accompanied by extravasation. As evidences of the inflammatory character of the process, we may adduce the anatomical changes in the serous membrane itself, the nature of the collected fluid, which does not usually consist of pure blood, and also the clinical course during life, which is, as a rule, febrile (comp. Description of the Disease). The terms "*pericarditis* or *pleuritis* exsudatoria sanguinolenta, and *pericarditis* or *pleuritis* scorbutica," seem, therefore, in general appropriate for these localizations of scurvy. The question whether cases of pure hæmothorax or hæmopericardium do not also sometimes occur, in which there is simple hemorrhage without inflammation, must

for the present be left unanswered, since we are unable to find anatomical proofs of this in the literature of the disease. With regard to the mode of origin of these hemorrhagic exudations, some authors hold that the bleeding is the primary pathological process, while the inflammation is consecutive to and directly caused by the hemorrhage (Samson-Himmelstiern, Seidlitz, Duchek, and others). Although we do not by any means wish to deny that the extravasation of blood into the serous cavity may, at times, actually excite inflammation of its walls, and that the extravasated blood itself may act as the exciting cause of the inflammation, nevertheless the other theory does not seem to us to offer a less plausible explanation of the scorbutic affections in question. This theory is, that the hemorrhage is only the consequence of a pre-existing inflammatory hyperæmia, and of the increased fragility of the capillaries occasioned by the inflammation. We should unquestionably give this latter theory the preference in the majority of the cases in which the extravasation takes place gradually, and more especially in those in which the exudation contains only a smaller quantity of blood. In many of the acute cases, on the other hand, in which, as Krebel states, a copious effusion can often be found in the pleura or in the pericardium, after the expiration of only a few hours, and in which, moreover, the subsequent autopsy shows that the fluid is almost pure blood, the assumption of a primary abundant hemorrhage with consecutive inflammation would probably be more correct. As yet we have no positive knowledge of the exciting causes of pleuritis and pericarditis exsudativa sanguinolenta, or of the primary hemorrhages which lead to their development in some cases. The assertions of Seidlitz, Krebel, and others, that cold, damp weather and the existence of the so-called "rheumatic constitution" are particularly favorably to the development of these processes in scorbutic patients, would, even if we were to concede them to be correct, apply rather to the case of primary inflammation with subsequent hemorrhage than to that of initial hemorrhage with consecutive inflammation. The signification of these etiological factors must not, however, be estimated too highly. Even supposing that we were willing to admit that many of the cases of hemorrhagic pleuritis, which

have been observed in scorbutic patients, were rather mere accidental complications of the pre-existing disease, due to subsequently "catching cold," or to the influence of a "genius epidemicus rheumaticus," we should scarcely attempt to explain in a similar manner the much more frequently observed sanguinolent inflammations of the *pericardium*. For we know from experience that a primary "rheumatic affection" of this latter serous membrane in healthy persons is extremely rare. In attempting, therefore, to explain the peculiar fact that hemorrhagic inflammations of the serous membranes, and especially of the pericardium, are relatively frequent in the course of scurvy, and are often, as it would seem, developed spontaneously, we are compelled to take refuge in the assumption that in scorbutic patients the serous membranes, and especially the pericardium, like many of the other tissues, are more strongly *predisposed to inflammation than the same parts in healthy subjects*, and that it only requires the stimulus of very trifling and consequently easily overlooked or perhaps unknown causes, to light up *actual* inflammation in these membranes. All the *scorbutic affections of the eye*, which were briefly studied in the general description of the disease, also belong in the category of hemorrhagic or hemorrhagic-inflammatory processes. They are consequently entirely conformable in character to the localizations of scurvy in other parts and organs, which we have just discussed. The fact that the external covering of the eyeball, namely, the conjunctiva, is most frequently the seat of the extravasation and inflammation, may unquestionably be satisfactorily explained by the exposed situation of this membrane.

We have finally to investigate briefly a few pathological phenomena which were mentioned at the close of the section on general symptomatology. In their anatomical and clinical characteristics these do not correspond exactly with the phenomena that we have thus far been studying, but they are nevertheless worthy of attention because of their frequent, and in part, perhaps, regular connection with the disease. One of the symptoms of this sort, which is frequently but by no means regularly met with, is the *enlargement of the spleen*. The signification of this symptom in scurvy can as yet be only very indefinitely and

indeed negatively determined. When it is developed in the course of the disease—apart from those cases where it arises from certain complications, especially malarious infection—it seems to depend not so much on the mere fact of the existence of the scurvy, as more particularly on the severity and intensity of the affection. At the same time, however, there have been a good many exceptional cases where, although the disease is very severe and extensive, the spleen remained small and was found at the autopsy to be of normal size. In the fatal cases, in which an enlargement of the spleen was developed during the course of the disease, and where the post-mortem examination rendered it possible to ascertain exactly the nature of the anatomical alterations, these were found to consist in hyperæmia of the organ, with pulpy softening of its tissue. The scorbutic enlargement of the spleen may consequently be classed with the acute enlargements of the spleen that are apt to occur in the course of typhoid fever, recent intermittent fever, acute miliary tuberculosis, and other febrile-infective processes. It does not, however, seem to us by any means allowable to assume on this account some toxic, infective principle as the cause of these and other cases of scurvy. The anatomical lesion in question is certainly worthy of notice, but it cannot serve in any way to explain the nature and pathogenesis of the disease. 2. The *albuminuria* also, as we have already mentioned, is for the most part only found in severe cases of scurvy. It frequently occurs as a pathological symptom in cases in which no anatomical lesion of the kidneys can subsequently be demonstrated. We believe ourselves justified in assuming that the form of albuminuria, which is not due to a complicating degeneration of the kidneys, really deserves the name of scorbutic albuminuria, and is dependent upon delicate *vascular* changes in the kidneys. We are still unable to demonstrate these changes anatomically, but they are nevertheless sufficient to permit a filtration of the albumen of the blood from the vessels into the urinary canals. We believe, therefore, that we have to deal here with the same nutritive or functional alteration of the walls of the blood-vessels, which must be assumed as the cause of the general hemorrhagic diathesis in scurvy. When this alteration is more highly devel-

oped in the uropoetic apparatus, it gives rise to the phenomenon of hæmaturia. Finally, in cases of albuminuria, where marked degeneration of the kidneys was found after death, the genesis of the former of course depends directly on the existence of the latter. 3. While we were describing the clinical picture of the disease, we mentioned further some *other interesting characteristics of the urine*, which Duchek discovered during his examinations of this excretion in the various stages of the disease, and which he asserts to be regularly present. The decrease in the quantity of the urine and of most of its solid constituents, as long as the disease is growing in intensity, and the converse increase of the quantity and of the solid matters in the period of defervescence, can both be pretty easily brought into genetic connection with the changes which the heart's action, and probably also those which the entire processes of nutrition, undergo in the different phases of scurvy. As with the increase of the scorbutic cachexia the action of the heart becomes weaker, and the nutritive changes, in consequence of the enfeebled circulation, become more and more sluggish, the urine in an equal ratio becomes less abundant and the total amount of its solid elements smaller. Inversely the re-establishment of a more active circulation, and the increased activity of all the organic processes which accompany convalescence, must be attended by an increase in the quantity of the urine and in the amount of its solid contents. It is a noticeable fact, however, that in the cases examined by Duchek the phosphoric acid, and particularly the potassa, did not participate in the quantitative decrease of the other solid elements of the urine in the first period of the disease. On the contrary, at the height of the disease these constituents appeared to be relatively, and, in three of the six cases examined, even absolutely increased in quantity. If we assume it as granted that this excess of potash and phosphoric acid will in future be discovered with a certain regularity in scorbutic patients, and will be found to constitute a tolerably constant attribute of the disease, we may explain it in a variety of ways. In the first place, Duchek himself believes that the relatively abundant excretion of potassa in his patients, during the entire course of the disease, might very well have been occasioned by the use of food rich in

potassa (vegetables), with which they were generously supplied, and indeed that it was doubtless, in part at least, due to this. If this view be correct, however, the abundant excretion of potassa in the urine would then in our opinion be an indirect proof that relatively little of the potassa taken into the system and absorbed by the circulating fluid really remained behind in the body of the patient and was employed for organic purposes. Inversely, the not only relative but actual decrease in the excretion of potassa during convalescence, which was also demonstrated by Duchek, might be explained by the assumption that conditions which had meanwhile set in were more favorable to the assimilation of the potassa in the food. It is possible, however, as Duchek also suggested, that the absence of a diminution in the excretion of potassa and phosphoric acid during the earliest part of the disease might be due to a comparatively excessive disintegration of those tissues of the body which are rich in potassa and in phosphoric acid, such as particularly the red blood-corpuscles and the muscular fibres. It would consequently be an indication that, in spite of the interference with the nutritive changes in general, the waste of certain tissues that are rich in potassa and phosphoric acid still continues relatively great, if indeed it is not absolutely increased, as happened in three of the cases examined. Finally, an *absolute* increase in the amount of potassa excreted has recently been demonstrated to occur during the existence of *fever* as an actual symptom of the febrile process (Salkowsky, Senator); and it seems to us, inasmuch as fever is a very common occurrence in severe cases of scurvy, that it is at least possible, if not probable, that the observations of Duchek were made on patients who were at the time suffering with fever, and that the increased excretion of potassa may have been in part a simple febrile phenomenon. It is evident, then, that the facts adduced by Duchek are capable of very various explanations, and for this reason they do not for the present afford us any secure standpoint for the development of a definite theory of scurvy. Nor are we disposed to agree with Duchek in the opinion that they are calculated to remove an objection to Garrod's hypothesis, which suggests a diminution in the quantity of potassa taken into the system as be-

ing the cause of the scurvy, and that they furnish at least a negative proof for it. So long as exact comparative observations are entirely wanting in regard to the quantities of potassa taken into the system and excreted by scorbutic patients who are free from fever, it will not be permissible to conclude, from the non-appearance of a diminution of the excretion, that the potassa goes through its permutations in the system, in all respects in a regular manner. It will be much better to leave the question in regard to the amount of potassa assimilated and excreted during this disease, for the present entirely open, and to await the result of more decisive examinations.

Finally, we return once more to the conditions of temperature in scorbutic patients, in order to call attention to the fact that the thermometric curve does not by any means conform to a constant rule in the individual cases. It may be confidently stated, however, on the basis of actual observations, that scurvy is in itself not a febrile disease, but that, on the contrary, fever is only an accidental and intercurrent, although an exceedingly common symptom. It occurs particularly in the more severe cases as a consequence of existing inflammatory localizations of the disease, and then continues during a shorter or longer period. In such cases, therefore, it is proper to speak of a "fever of individuals suffering with scurvy," but not of a "scorbutic fever."

Nature and Pathogenesis of the Disease.

At the beginning of this chapter, we defined scurvy to be a general derangement of nutrition, in which, in addition to a more or less severe, and at the same time peculiarly modified cachexia, hemorrhagic and hemorrhagic-inflammatory localizations occur in various organs and tissues. The analysis of the symptoms of the disease which has just been terminated, has, we think, demonstrated by details the correctness of the general definition previously given, and has particularly furnished proofs that the characteristic local symptoms of the disease can all be considered as the results of a definite, general, morbid condition; or, in other words, of a constitutional anomaly of the body.

The constitutional nature of the disease is still more clearly demonstrated by the pre-existence of the scorbutic cachexia, which, as a rule, at least precedes by some space of time the local eruptions. When considered in connection with this initial affection of the entire body, the later local phenomena appear for the most part only as further partial perturbations of a derangement of the organic processes, which involves the entire system. The *clinical form* of these partial lesions is, however, as we have shown, double: either the inflammatory diathesis goes hand in hand with the hemorrhagic diathesis, or, along with an unusual tendency to extravasation of blood per rhexin, and probably also per diapedesin, there exists an abnormal vulnerability of most of the tissues, in consequence of which inflammation is very readily excited in them by slight injuries of any kind, or even, as it would seem, appears spontaneously. The character of the inflammations thus produced is, however, for the most part, also hemorrhagic; either the inflammatory hyperæmia leads to extravasation from the brittle or abnormally permeable capillaries, or, on the other hand, the extravasation acts as an inflammatory irritant to the tissues with which it comes in contact. Everything considered, therefore, scurvy is a hemorrhagic, constitutional disease, in which, to distinguish it from other forms of the hemorrhagic diathesis, the cachectic nature is strongly marked, and at the same time the tendency to inflammatory lesions of the tissues is very great.

The etiology of the disease shows, moreover, that it is not a congenital constitutional anomaly, like hæmophilia; nor is it, like the latter, transmissible from father to son, or, in the majority of cases, hereditary; on the contrary, the disease is first acquired after birth, under the influence of certain antihygienic conditions to which, as a rule, not single individuals alone, but whole bodies of men at once are subjected; hence, it commonly appears in the form of extensive or circumscribed epidemics, seldom in isolated cases. It would be incorrect, consequently, to seek for the essence of scurvy, like that of hæmophilia, in some vitium primæ formationis. On the contrary, it is fair to assume that the anomalies in the vascular system developed at a later period, and the diminution of the physiological

resistance of the tissues to inflammations, both of which are observed in scorbutic patients, are the results of an alteration in the nutritive process, occasioned by the outward circumstances of existence of the individual. Hence, the answer to the question as to the pathogenesis of scurvy would essentially depend upon the discovery of the manner in which, under the influence of the causes discussed by us in the section on Etiology, the normal nutritive process may become so altered in the vessels and the tissues supplied by them, that hemorrhages readily occur and inflammations are easily developed.

In the first place, we must here insist on one thing, viz., that as the etiology of the individual cases or epidemics of scurvy is notoriously not always exactly the same, so the pathogenesis cannot with any more reason be *a priori* considered to be the same for *all* cases. We must clearly understand that the insufficient power of resistance and the permeability of the capillaries, as well as the vulnerability of the tissues, can, as we know by experience, not only be occasioned by very various injurious influences, but possibly, too, in very different ways by these various causes. Our theoretical speculations will unquestionably reach a plausible result more rapidly if we investigate, first, the possible mode of action of those pernicious agencies whose influence in exciting scurvy has been positively demonstrated in an empirical manner by numerous and exact observations, leaving the remaining agencies, known to be prejudicial, for subsequent consideration.

It was in this way, as we have already repeatedly stated, that Garrod proceeded, when he erected his so-called *potassa*-theory of the disease upon the basis of the thousandfold authenticated fact, that scurvy is developed with the greatest facility among persons who are deprived of a fresh vegetable alimentation (green vegetables, potatoes). Since those aliments, on the total absence of which from the food the scorbutic cachexia with its secondary local consequences most frequently depends, are specially rich in potassa, and contain, moreover, this alkali in a form particularly easy of assimilation (in combination with carbonic or some vegetable acid), Garrod further concludes that the scorbutic affection is due chiefly to an *insufficient supply of potassa in the organ-*

ism.—It cannot be denied that this theory is in several respects very seductive; it not only seeks to do justice to the special physiological nutritive value of numerous articles of food, which contain otherwise very little nutritive matter, in the usual sense of these words, and the deprivation of which for this very reason is not in fact followed by ordinary marasmic anæmia, but it is also supported by weighty facts derived from the chemistry of the tissues. These facts prove that a deprivation of potassa is by no means a matter of indifference to the organism. For, little as is otherwise known in regard to the special physiological importance of most of the inorganic nutritive substances, and in particular of the potash combinations, these two facts are positively settled, viz., that potassa forms an integral constituent of all tissue-elements (cells), and that precisely some of the tissues which are physiologically of the greatest importance, such as the muscular fibres and the red blood-corpuscles, are especially *rich in potassa.*

If we take these facts into consideration, it will certainly be easy to understand that an insufficient or inappropriate supply of potassa in the food would not presumably be without a pathological action on all the tissues of the body, and especially upon such as contain large quantities of potassa. At first the physiological function of the tissue, and its normal physiological resistance to causes of disease of every kind, will be impaired, and later on, the deprivation of potassa continuing, the physiological reproduction of the tissue-elements will probably be checked. It surely needs no further demonstration to show that both the disturbance in the subjective and objective general condition, and also many of the special peculiarities of the scorbutic cachexia—for instance, the very pronounced functional derangement of the heart and the voluntary muscles—the tendency, moreover, to inflammatory lesions of the tissues terminating frequently in ulceration, etc., and finally, also, the oligocythæmia which gradually makes its appearance in the later stages of the disease, can readily be accommodated theoretically with this view. Referring now particularly to the hemorrhagic diathesis in scurvy, and to its possible connection with the insufficient supply of potassa to the organism, we may either assume a

direct trophic impairment of the capillary walls, or what is more probable, an indirect impairment of their function and nutrition through the red blood-corpuscles. These latter being less rich in potassa, and thus weakened in constitution, are no longer able to accomplish the task of keeping the capillary walls in a state of functional and nutritive health.

This is not, however, the place to lose ourselves in further conjectures. We must simply endeavor to deduce a really pathological cause from the *pathogenetic* influence which is in all probability furnished by insufficient supply of potassa to the organism, and which possibly also has a direct etiological action in very many cases of scurvy. It is evident that it is *not the insufficient supply of potassa, nor the presence of this substance in too inconsiderable quantities in the circulating fluid*, but the *consequent want of potash in the tissues themselves*, which must be regarded as the real morbid condition and as the cause of the perverse (functional, nutritive, and plastic) behavior of all the tissue-elements, including naturally the red blood-corpuscles, or the elements of the blood-tissue. Any series of experiments, therefore, which might be undertaken with the object of obtaining, on the basis of Garrod's hypothesis, an anatomical and chemical substratum for the understanding of scurvy, must aim at determining the comparative quantities of potassa contained in the red blood-corpuscles, the muscles, and other tissues in healthy persons, and in scorbutic patients. They must not, however, be limited entirely to analyses of the blood as a whole, since these would only furnish proof of the condition at a given moment of the general nutritive fluid, which constantly varies in the percentage of its component elements. Although no comparative investigations of this sort have as yet been made, and Garrod's theory is on that account unfortunately still unprovided with a firm anatomical basis, it may nevertheless be profitable, with a view to the establishment of the possible mode of origin of scurvy, to devote a short space to the hypothesis that a want of potassa in the tissues, or *a want of organic potassa* (*not* of potassa circulating in the fluids), may bring on the scorbutic disorder. Evidently this latter theory affords a much more reliable basis

for a comprehension of the pathogenesis of individual cases of scurvy than the theory which only takes into account an insufficient *supply of potassa* to the organism, for it does not seek to explain *how the want of organic potassa has been occasioned in the concrete cases.* An insufficient supply of potassa in the food *is one, but by no means the only possible way* in which this absence of potassa in the tissues can be produced. It will not be uninteresting, and is, indeed, necessary, to consider here briefly some of the other possible ways in which it can be produced; in doing so we shall take the opportunity to reconsider some of the empirical statements made under the head of Etiology.

A want of potassa in the tissues can *in the first place* also be due to the fact that the potash combinations are supplied to the circulating fluid by the food in sufficient quantity, but in a form that is ill adapted for assimilation. In this case they are soon discharged from the body in the excretions, without having previously been appropriated by the tissues, and thus without having fulfilled their physiological purpose. In this connection the remark of Chalvet, a decided advocate of the potassa theory, is worthy of notice. He explains in this way the fact that green vegetables and potatoes are so much more valuable as anti-scorbutics than the dry leguminous vegetables and meat. He believes, moreover, that the deprivation of the first-named articles of food is the most pregnant cause of scurvy, simply because they contain potassa in the unstable, and, therefore, easily assimilable form of potash, and also in combination with the vegetable acids, while the same alkali exists in meat, dried leguminous vegetables, and bread, in considerable quantities, it is true, but in the much more stable forms of chloride of potassium and phosphate of potassa. Garrod, too, relying on his often mentioned investigations of the chemical constitution of various articles of food, pronounced decidedly in favor of taking the percentage of *potash* in them as the measure of their antiscorbutic properties, and, as we mentioned on page 134, chose particularly the remarkably high figure of the carbonate of potassa in the potato as the point of departure in his theoretical speculations. *In the second place*, a deficiency of organic potassa may arise in spite

of an abundant and appropriate supply of potassa in the food, when derangements of the digestion exist accompanied by diarrhœa. The food which is taken into the stomach is, under such circumstances, prevented from entering the circulating fluid in sufficient quantities. The question whether the predisposition of dysenteric patients, and of persons suffering with diarrhœal dyspepsia, to scurvy, as well as the development of the affection after the ingestion of decomposing articles of food and of foul water, may not be due to this circumstance, must for the present be left unanswered, although it must be borne in mind as a possibility. *In the third place*, the taking up of the circulating potassa by the tissue-elements must also undoubtedly be influenced by all those weakening agencies which lessen the trophic energy of the cells, and diminish their capacity to appropriate the potassa from the blood. As instances of these influences, we may mention deprivation of fresh air and light, idle repose of the body, and excessive heat. We have already stated that these external pernicious influences are also counted among the causes of scurvy, and, with good reason, as it seems to us, always find a place in the etiology of this disease. In defence of the explanation of their mode of action, which we have just attempted to give, we will merely refer to that fundamental cellular principle, according to which the taking up of different substances from the blood into the living cell-body is a vital action of the latter (Virchow). It is therefore possible that even the most abundant supply of potassa from without may be useless, if, in consequence of great prostration of the patient and exhaustion of the nutritive energies of the tissues, the cells no longer possess the power to extract from the stream of nutritive matter which flows by them the substances necessary for their own regeneration. It certainly seems right to hold up all these possibilities to the view of the opponents of the potassa theory, who might otherwise with apparent reason base their opposition on the fact that scurvy has at times occurred among persons supplied with food containing potassa in abundance, and has even persisted under these circumstances (for instance, the epidemic of Rastatt). These possibilities present the theory in a somewhat different light, namely, under the

form which we have just described, and which is decidedly more appropriate for such cases as the above. It is sufficient simply to mention the facts, *that the distance which the alimentary substance containing potassa has to travel in passing from the mouth to the tissue-elements is considerable*, that it is readily turned aside from the direct course, and finally, that even when it has safely arrived at the cells, it is not always necessarily absorbed into them.

It is evident that the amount of potassa contained in the tissues must depend on the quantity consumed in, as well as on the quantity taken up by, the tissue-elements. Hence whenever, in consequence of unusual activity of the organic processes, a large quantity of potassa is temporarily discharged from the tissues into the circulating fluid, whence it is eliminated through the excretory canals, the demands of the body for a more abundant supply of potassa must of course be particularly great, and a non-compliance with these demands will probably easily give rise to morbid disturbances, and in particular to scurvy. It would be exceedingly interesting, and it is even important, to know, for instance, how the expenditure of potassa during severe bodily exertion compares with that during a state of repose, and further, how the amount consumed during a long continued sojourn in a damp, cold atmosphere would compare with that consumed during a sojourn of equal length in a temperate or warm and dry climate; since hardships and damp, cold weather have been so frequently asserted to be exceedingly active accessory causes of scurvy. As, however, no direct investigations of these points have as yet been made, it is for the present unfortunately impossible to test the soundness of the potassa theory in these respects. The decision of the question, whether or not that theory suffices to meet these etiological demands, must await the results of further research. Finally, we will also mention that the increased excretion of potassa during *fever*, demonstrated by Salkowsky,[1] teaches us at least *one* important fact, viz., that the amount of potassa consumed under definite *pathological* conditions does not by any means conform to the amount

[1] Virchow's Archiv. Bd. LIII. 2. 3. 1871.

of potassa supplied, but follows solely its own laws. Whether or not there are also *physiological* conditions which, in regard to the waste of the potassa of the tissues, are analogous to fever, is a question that is not answered by the investigations of this observer, since these, so far as they relate to healthy subjects, have been directed only to the influence of the food—that is, of the supply of potassa—upon the excretion of this substance.

Although, however, the results of Salkowsky's investigations cannot as yet be made use of to determine theoretically the varying predisposition of healthy persons to scurvy under different conditions of existence, we may at least deduce from them the conclusion that there is an increased predisposition to scorbutic symptoms on the part of fever patients and of convalescents from febrile diseases. In fact, observations at our disposal seem to prove that individuals who are enfeebled by some severe disease are more rapidly attacked by scurvy than those whose powers of resistance are in the normal physiological condition. Some exquisitely marked febrile affections, for instance, particularly intermittent fever, occasion in fact an unusually intense predisposition to scurvy. Duchek is inclined to ascribe the frequent occurrence of scurvy as a complication of malarial fever, which he has himself observed, to the extremely rapid destruction of the red blood-corpuscles (in other words, to the extensive disorganization of a tissue peculiarly rich in potassa) in intermittent fever. This destruction does not seem to be due entirely to the fever; it is, in part at least, the effect of the specific infection itself.

In what precedes we have sought to secure for Garrod's potassa theory of the pathogenesis of scurvy all the domain which it is able, under whatever circumstances, by virtue of its own inherent plausibility, to hold in subjection. We have, moreover, endeavored particularly to show that a number of cases and epidemics of scurvy, in the production of which a scarcity of food rich in potassa was notoriously not an active factor, can also, to some extent, be explained by this theory; but we nevertheless do not wish to be understood as having in the least degree prejudged the question as to the possible modes of origin of these cases. For instance, we do not by any means wish the preceding deduction to be understood to mean that, in our opinion, the syndrome of scurvy *must* of necessity be the result of a scarcity of potassa in the tissues in all those cases in which there is a high degree of probability, or even only a remote possibility, of the existence of this pathological alteration. We do not deny that the disease might possibly in some, or, indeed, in very many of these

cases, have originated from very different morbid factors. How far the casuistical domain of that theory actually extends, and whether it really possesses any such domain, are questions for answers to which we must look to future investigations. The direction which it is desirable for these investigations to take has been described above. Meanwhile, it will certainly be well in any case to bear in mind the possibility that the scorbutic symptoms may not always take their origin in the same derangement of the general nutrition, but that not only the pathogenesis and the etiology, but also the chemico-pathological substratum, may perhaps vary in individual cases. In view of the facts here discussed, the assumption may seem plausible that a want of the needful quantity of organic potassa may influence injuriously the integrity of the tissues and with it the health, and that the special form of the derangement of the health thus occasioned is in every case the scorbutic. On the other hand, however, there is nothing in them which offers the least contradiction to the hypothesis that precisely the same combination of symptoms, namely, a general cachexia, accompanied by hemorrhagic inflammatory localizations in different tissues, might at another time be produced by trophic derangements of quite a different character, such, for instance, as those occasioned by miasmatic poisoning. It must always be remembered, that the disease known in pathology as "scurvy" for the present forms only a symptomatic unity, and that the name of the disease is strictly considered not much more than the conventional, short expression for a special collection of morbid symptoms. If we bear this in mind, we shall be able to restrain ourselves and others from premature and perhaps entirely hopeless attempts at unification on an etiological, pathogenetic, and chemico-pathological basis.

Complications and Sequelæ.

It has been already noted in the etiology that scurvy not infrequently attacks individuals who are already suffering from disease, and then itself plays the part of a complication of the pre-existing pathological process. We have also named at the

appropriate place those affections, such as malarial diseases, dysentery, and syphilis, which show a peculiarly marked tendency, where the conditions are favorable for the development of scurvy, to become complicated with this disease. At other times the secondary scorbutic affection seems to be merely an accidental complication of the pre-existing fundamental disease, since the empirical proof of a more frequent coincidence of the two cannot be adduced. In this connection it is necessary to state briefly the fact that scurvy may occur as a complication during the course of the most diverse morbid processes. The modifications which this complication occasions in the clinical character of the pre-existing disease are almost always of an unfavorable nature. The derangement of the general health then almost invariably becomes more marked, and the signs of a pronounced cachexia usually appear very rapidly; but aside from these, the hemorrhages which now occur in loco affectus, as well as in other parts of the body, have their effect in aggravating the condition, and may even be the direct cause of a fatal issue of the primary disease. This is apt to be the case, for instance, when scurvy supervenes as a concomitant constitutional anomaly, in the course of dysentery, typhus, pneumonia, phthisis, and inflammations of the serous membranes, particularly pleuritis, and finally, when it complicates suppurating and granulating wounds, fractures, and inflammatory diseases of the joints. Observers have had opportunities on many different occasions to convince themselves of the increased malignity of all sorts of severe affections, both internal and surgical, in the contingency just described.

On the other hand, convalescents from scurvy, and patients who are still suffering from the disease, are liable to be attacked by other diseases. In such cases we have, of course, to deal with complications or with sequelæ of the scorbutic affection itself. These secondary affections, again, may be entirely accidental, having no demonstrable genetic connection with the existing or antecedent scurvy; in other cases, as some observations at our command prove, a connection of this sort can be traced to a certain extent. With regard to the accidental complications and sequelæ, which may be very diverse in their nature

and cannot here be enumerated in detail, we may make the general statement that they run a much more severe course than under ordinary circumstances. The reason of this is to be found in the fact that they are developed, not in a healthy organism, but in one that is shattered and exhausted by the cachexia, which is either still in full force, or at least has not yet been entirely overcome. Naturally, those cases are relatively most unpropitious in which the scurvy itself is not yet eradicated, and the supervening complication is inherently severe in its nature. The case is more propitious when less serious affections occur as accidental sequelæ of a scurvy that has already run its course. In the true complications, independently of the great exhaustion of the patients, the hemorrhagic-inflammatory diathesis especially exerts a disturbing and dangerous influence on the regular course of the affection, while in the sequelæ it is the anæmia that has been left behind by the antecedent scurvy, and constitutes in fact a secondary constitutional affection, which is the principal cause of the diminished power of resistance on the part of those attacked. We must content ourselves with this brief mention of the principal traits in the clinical behavior of such accidental processes, since a closer investigation of their details does not seem to us to be in place here.

Among the complications of scurvy which are observed with relative frequency, and which consequently have perhaps a more direct connection with the scorbutic affection, we must mention, on the part of the respiratory apparatus, particularly *croupous pneumonia.* At least, it is not very unusual to find at the autopsies of persons who have died of scurvy, the anatomical signs of a more or less recent hepatization of extensive portions of the lungs. In other cases the subjective and objective chest-symptoms during the lifetime of the patients indicate the acute development of a pneumonic process. The pneumonia of scorbutic patients runs, as a rule, a very severe—for the most part, indeed, a fatal course. The immediate cause of death is apparently, in most cases, the extreme insufficiency of the heart's action—a direct effect of the existing scurvy, which from the very beginning impresses on the supervening pulmonary affection an adynamic character. Sometimes, too, at the height of

the disease, before the fatal issue, mortification of the tissue of the lungs sets in with the characteristic signs of pulmonary gangrene (stinking, discolored sputa). In such cases the autopsy shows, in addition to the pneumonic infiltration, gangrenous foci of greater or less extent in the midst of the hepatized tissue. *Hemorrhagic infarction* is also a frequent complication of scurvy. The infarctions are usually multiple, and the anatomical changes characteristic of them are often found in the lungs at the autopsy. The mode of production of these foci is, as a rule, the same in scurvy as under other circumstances—namely, by *embolism;* the emboli are derived from thrombi which form in the right auricle, and particularly in the appendix auriculæ, in consequence of the enfeebled circulation.

The *acute, ulcerating valvular endocarditis*, which is sometimes, but not often, found at the autopsies of scorbutic patients, should probably be regarded as a merely accidental complication, occasioned perhaps by septic infection originating in scorbutic ulcers of the skin or wounds. In the majority of the cases of scurvy that terminate fatally, the valves have been found perfectly intact, although blowing murmurs over the heart are very frequently heard during life. *Hemorrhagic pericarditis*, like the analogous form of pleuritis, and of the less frequent peritonitis, must be classed among the localizations of scurvy, since they belong with those lesions which, although they may occur exceptionally under other circumstances, are essentially characteristic of this disease, and are very commonly found at the autopsies of severe cases. We have also already had occasion to speak of the relation which the occasionally observed *diphtheritic-ulcerative enteritis* bears to the scurvy. We pointed out, in particular, that this process, which is almost always attended by violent symptoms, especially by frequent discharges of blood per anum, and rapidly leads to a fatal termination, must at times, like hemorrhagic pericarditis, and other hemorrhagic forms of inflammation, be regarded as merely a localization of the existing general disease, while in other cases, on the contrary, it is an actual complication due to infection with *dysenteric* poison.

On the part of the *kidneys*, we must mention the existence of

parenchymatous degeneration in a considerable number of those cases of scurvy in which albuminuria existed during life (Cejka, Krebel). We have already expressly stated, however, that in quite as many of the cases, where albumen appeared in the urine, gross alterations in the kidneys were entirely absent.

Finally, of the complications of scurvy which affect the *nervous apparatus*, we must mention an anomaly of sight—namely, *hemeralopia.* The connection of this peculiar morbid phenomenon with scurvy has been, both in former times and quite recently, the subject of active discussion. In the first place, it is a fact that hemeralopia and scurvy have been very frequently found coexisting in the same persons; usually the scurvy is developed first, the patients subsequently becoming hemeralopic. It is also true, however, that numerous and widespread epidemics of scurvy, as well as a great number of smaller outbreaks, have run their course entirely without hemeralopia; and that, finally, hemeralopia has also been repeatedly observed alone without scurvy. In our judgment, therefore, both those authors who simply deny any and every connection of night-blindness with scurvy (Friedel), and those who maintain that hemeralopia is, without qualification, to be set down as a phenomenon of scurvy (Delfort, Blanc, Bumpfield, Hulme, and many others), are equally in the wrong. The most that can be concluded from the facts at our command is, that, among the as yet but little studied causes of hemeralopia, there are some which relatively often exist side by side with, and are perhaps, indeed, in part identical with the causes of scurvy, and that, under such circumstances, an epidemic of hemeralopia as well as one of scurvy frequently arises (Bryson, Schwarz, and others); or, perhaps, that the existing scorbutic cachexia itself develops a strong predisposition to hemeralopia (Kuettner,[1] Duchek). In point of fact, it seems to us that *both* these possibilities must be admitted to have a part in producing the effect in question, since either one of them alone is hardly sufficient to explain it. On the one hand, the facts that in the frequent cases of coexistence of scurvy and hemeralopia in one and the same circle of men, usu-

[1] Petersburger med. Zeitschrift. Bd. VI. S. 65.

ally only scorbutic persons were attacked by the derangement of the sight, healthy persons escaping (Schwarz, Kuettner, Duchek), and that, as repeated observations prove, the hemeralopia disappeared under an exclusively antiscorbutic treatment either simultaneously with or soon after the scurvy (Schwarz, Kuettner), demonstrate conclusively the existence of a genetic connection between the two diseases. On the other hand, however, the occurrence of entire epidemics of scurvy without a single case of hemeralopia, and the analogous occurrence of isolated hemeralopia without scurvy, prove that, in addition to the usual causes of scurvy, other peculiar concomitant causes must be present to occasion de facto the derangement of vision in the patients who are already predisposed to it. At present it is unfortunately still impossible to describe more closely the nature of these special genetic influences, and also to say on what the predisposing influence of scurvy actually depends. It does not seem to us altogether correct to consider the hemeralopia as simply the effect of the prostrated condition of the general nutrition (Duchek), since anæmic marasmus does not of itself usually lead to hemeralopia in other cases.

The occurrence of hemeralopia in the course of scurvy is not confined, as it was once thought, to epidemics of scurvy at sea and in the tropical regions; it has been also observed in recent times in epidemics on land, and where the disease has prevailed on shipboard in the temperate zones. Thus, it was observed in numerous cases during the epidemic in the work-house at Prague (Cejka), and during the epidemic at Rastatt (Opitz); it was also observed by Kuettner, in the prison at St. Petersburg (1864), in 18 out 140 of the prisoners who were suffering from scurvy, etc. It was also met with as a complication of scurvy, according to the reports of the English navy, not only at tropical fleet stations, but also at the naval stations in the Mediterranean and in the irregular service (Friedel). It was, however, much more frequent at the tropical stations. These reports, nevertheless, show that the hemeralopia is not immediately dependent on the scurvy. For, at the Australian station, where, during the period of twenty years from 1845–1865, scurvy was most prevalent in the English ships, hemeralopia was entirely absent, whereas at three other stations this disorder occurred more frequently than the scurvy. Both affections, therefore, present evident points of contact and even very remarkable coincidences, but, on the other hand, in many cases such disparity of behavior that it is as yet exceedingly difficult to determine with any accuracy their relations to each other.

Diagnosis.

The diagnosis of scurvy does not in general present any great difficulties. As the disease rarely attacks isolated individuals, and usually occurs in the form of an epidemic on shipboard, in fortresses, or in camps, or as a prison or asylum pestilence, the individual case of scurvy under observation is, as a rule, only one among several or many. This *cumulation of similar affections*, within certain limits of time and space, facilitates in no small measure the correct diagnosis of each new case. It is a very noticeable fact that those affections with which scurvy in its clinical manifestations presents the closest resemblance, and for which it might most readily be mistaken, namely, hæmophilia and morbus maculosus (see the following chapter), behave in this respect in a totally different manner. The other diseases of a hemorrhagic character which might perhaps, in addition to the two just named, come into question in the differential diagnosis, namely, leukæmia, pseudoleukæmia (anæmia splenica et lymphatica), and progressive pernicious anæmia, do not belong in the category of pestilences.

The *etiological conditions* also are of value in aiding to establish the diagnosis. Scurvy is in the first place, as we have already frequently remarked, unlike hæmophilia, neither a congenital or hereditary disease, nor an habitual anomaly of the constitution; on the other hand, unlike the majority of the cases of morbus maculosus, its origin is not apparently spontaneous. On the contrary, in almost every epidemic of scurvy, and also pretty constantly in the less common isolated cases of the disease, the anamnesis proves that the bodies of men or the single individuals attacked have been previously exposed for a shorter or longer period to the influence of certain anti-hygienic conditions. While speaking of the etiology, we described in detail the special nature of the pernicious influences which produce scurvy. At present, therefore, it will be sufficient to recall briefly to the memory of the reader the most important of these. First in importance is the want of fresh vegetable food; in the second rank we may mention the want

of fresh meat, the use of spoiled food, and putrid drinking-water, a long continued sojourn in close, damp, and dark quarters, or in the open air during damp, cold weather, with insufficient clothing, over-exertion of the bodily powers, depression of spirits, etc. The amount of consideration which is to be paid to these anti-hygienic conditions, in making the diagnosis, must correspond with the greater or less degree of importance which they possess as causes of the disease. When we have to deal with isolated cases, the diagnosis of scurvy should, as a general rule, not be definitively made unless it is justified, not only by the entire clinical picture, but also by the etiology of the existing affection.

Among the *local symptoms* of scurvy, the peculiar *affection of the gums*, with its previously mentioned characteristics, must be put prominently forward as important for the diagnosis; not only because it is by far the most frequent, and for the most part, too, the earliest of all the localizations of the general disease, but also because it is almost never met with in precisely this particular form, in any other hemorrhagic disease than scurvy. It is true that simple bleeding from the gums is by no means rare in hæmophilia, and even in morbus maculosus, and that it is also observed quite frequently in the course of leukæmia, pseudoleukæmia, progressive anæmia, etc. In all these morbid conditions, however, we almost invariably miss that inflammatory loosening and spongy consistency of the bleeding gums, which, together with the disposition to hemorrhage, form such regular characteristics of the scorbutic affection of the mouth. Leukæmia forms the only exception to this rule. In it we sometimes meet with a hemorrhagic inflammatory affection of the gums, the gross clinical picture of which seems, according to the description, to be similar to that of the stomatitis gingivalis of scurvy (Ollivier). Mosler ascribes it to the irritating action of the saliva, which in leukæmic patients becomes morbidly altered in its chemical constitution. This leukæmic stomatitis—in which, be it mentioned in passing, Ranvier has recently discovered by microscopic examination, in addition to interstitial extravasations of blood, a filling-up of entire capillary districts of the gums with colorless white blood-corpuscles—is,

however, of very rare occurrence, and even when present, it cannot, if proper care be exercised, easily lead to a confounding of the existing leukæmia with scurvy. For it seems that the affection of the gums in question only occurs exceptionally in very advanced cases of leukæmia, and in these cases the condition of the blood, as well as of the spleen and the lymphatic glands, always presents sufficiently clear proofs of the nature of the disease to dispel immediately any doubts which the physician might entertain.

On the other hand, however, as we have already mentioned, the affection of the gums may be entirely wanting in scurvy. This is especially apt to be the case when the patient has lost his teeth ; the part of the mucous membrane of the mouth in question is then usually very slightly or not at all affected. This irregularity in the type of the disease will not, however, prevent a correct diagnosis, provided only the disease be in other respects, as regards etiology and symptomatology, sufficiently well marked. Next to the gums, the *external skin* is unquestionably the part in which the localizations of scurvy occur with the greatest frequency ; and since the various purpuric eruptions which make their appearance on it are also undoubtedly the most perceptible to the senses of all the symptoms of the disease, it is natural that, altogether independently of their relations to the scorbutic affection of the gums, great importance should be attached to them in forming the diagnosis. We can certainly maintain, without fear of error, that the presence of an abundance of the hemorrhagic eruptions, which have been described in detail in another place, adds much to the security of the diagnosis of scurvy in individual cases. An entire absence of any and every purpuric eruption speaks with equal force against the existence of this disease. On the other hand, however, no pathognomonic signification can be ascribed to those forms of purpura which are most frequently observed in scorbutic patients, namely, to the *simple* hemorrhagic petechiæ, ecchymoses, and vibices, even though these more common kinds of interstitial cutaneous hemorrhages, like the inflammatory extravasations which will presently be mentioned, occur with especial predilection on the lower limbs, and are often limited entirely to

these regions of the body. It is well known that the pathological domain, within which such suggillations of the skin of greater or less extent may and indeed often do occur, is much more extensive than that of scurvy alone. Hence, even when the simple hemorrhagic eruption is exceedingly abundant, we can only conclude from it that a hemorrhagic diathesis exists in the case under consideration; for the exact diagnosis of the special variety of the disease, we must rely on the remaining symptoms, with what help can be derived from the etiology of the case. The case is somewhat different with the hemorrhagic inflammatory eruptions, particularly those which we have described in another place under the names of Pemphigus scorbuticus and Rupia scorbutica. These varieties of purpuric eruption, as is evident from the qualifying adjective we have used, occur, so far as is known, almost exclusively in scurvy—hardly ever in other hemorrhagic diseases; their presence, therefore, furnishes a much more certain proof of the existence of the former disease than is offered by the appearance of petechiæ, ecchymoses, and vibices. The syndrome of scurvy is still more characteristic in all those severe cases in which, in addition to the gums and the skin, other parts of the body and other tissues, namely, the subcutaneous stratum, the muscles, the serous membranes, the periosteum of the bones, and the articulations, are affected in the manner we have already described. We may state explicitly that neither the peculiar, board-like infiltration of the subcutaneous connective tissue, nor the hemorrhagic inflammatory foci in the muscles, nor the enormous effusions into the serous cavities, etc., which are so frequently met with in scurvy, combine with any frequency to form a united clinical picture in any other disease. It may therefore be affirmed, in regard to the local symptoms of scurvy, that the facility with which the diagnosis is made from them *alone* increases with the number of tissues affected, and the distinctness of the inflammatory as well as of the hemorrhagic character of the existing local lesions.

Finally, the *state of the general health* is also of very great importance in the diagnosis of scurvy; in many cases, indeed, it is absolutely decisive. In contrast especially to hæmophilia and morbus maculosus, two hemorrhagic diseases which are

characterized by the absence of any real cachexia, or in which, at least, a cachexia is only developed as a complication in the later stages, in consequence of the loss of blood, the great majority of the cases of scurvy, as we have already stated, are ushered in by a morbid derangement of the general health, which, in addition to a greater or less disturbance of the subjective sensations and of the capacity for bodily exertion, produces an exquisitely marked cachectic change in the appearance of the patients. It is usually only after this initial stage has lasted for a time—in other words, *after the cachexia already exists*, that the local symptoms of the hemorrhagic inflammatory diathesis break out in various parts of the body, especially in the gums and the skin, and, by their combination with the general derangement, complete the hitherto incomplete clinical picture of scurvy. It is evident, therefore, that, like the etiology and the local symptoms, the state of the general health also constitutes an important point of difference between most cases of scurvy on the one hand, and cases of hæmophilia and morbus maculosus on the other, and that it can be made useful in the differential diagnosis of these different, but nevertheless symptomatically related affections. It must, indeed, be admitted that in mild cases of scurvy the initial cachexia may be but little developed, or even almost entirely wanting; but nevertheless, this exceptional behavior in single cases must not by any means be thought to diminish the general trustworthiness of the diagnostic rule just formulated. On the contrary, for the correct appreciation of such anomalous cases, it is only necessary to take sufficiently into consideration the fact, that even when the cachexia is absent, the diagnosis can invariably be made with the greatest probability, provided the case in question occurs during the prevalence of an epidemic of scurvy, and evidently under the influence of causes that are liable to produce that disease; and provided, further, the existing hemorrhagic inflammatory local symptoms (in the gums, the skin, the subcutaneous connective tissue, the muscles, etc.) are of such a nature as to make any other diagnosis seem absurd.

On the other hand, the primary cachexia, which is almost always present in scurvy, produces a certain resemblance between

this disease, in its clinical behavior, and leukæmia, pseudoleukæmia, and progressive pernicious anæmia, in so far as the hemorrhagic diathesis in these three morbid processes is always developed secondarily to a severe general illness. Notwithstanding this, however, scurvy cannot be easily mistaken for leukæmia and pseudoleukæmia ; it is easier to conceive the possibility of its being occasionally confounded with pernicious anæmia, especially as unfavorable outward conditions of existence sometimes play a certain part in the etiology of this last process. In addition, however, to the fact that progressive pernicious anæmia has never yet broken out epidemically as a pestilence in any locality, there exist, as a rule, enough outward points of difference between it and scurvy, to distinguish clinically in a satisfactory manner each of these two diseases from the other, and consequently, to serve for a differential diagnosis. We may mention, for instance, in this connection, that patients with pernicious anæmia present an excessive pallor ; scorbutic patients, on the contrary, rather a cyanotic (livid) hue ; that, moreover, the bleeding in pernicious anæmia is a simple hemorrhagic phenomenon, while in scurvy it is frequently the accompaniment of local inflammatory processes, etc. Finally, useful diagnostic points can also be obtained ex juvantibus, since appropriate treatment is capable of producing extraordinary results in scurvy, while up to the present time every sort of treatment that has been tried in leukæmia and pseudoleukæmia, as well as in progressive pernicious anæmia, has proved almost entirely useless.

Duration. Terminations. Prognosis.

The *duration* of scurvy is scarcely ever short. It is influenced very essentially, however, by the outward circumstances in which the patients exist during the course of the disease. The longer, namely, the patient, after the attack has commenced, remains exposed to those anti-hygienic influences to which the development of the disease was especially due, the more severe does it usually become, and the longer, in particular, is its duration, supposing of course that the life of the patient is preserved, and that at some later period a favorable change takes

place in the conditions of his existence. When this change occurs, a turn for the better usually sets in rapidly, even in very severe and apparently desperate cases. Even then, however, a considerable time elapses in almost every case; and indeed, when the attack is very severe, many weeks, as a rule, pass by before the disease can be considered as ended and the bodily powers as fully restored. When the disease terminates fatally, its duration is, it is true, more or less shortened by the decease of the patient; still it is in general rare for death to ensue very soon after the scorbutic symptoms make their appearance. The rule is rather that the really dangerous accidents which bring about the dreaded catastrophe only appear after the symptoms have persisted for a considerable length of time.

In recent times, since we have learned how to guard better by prophylactic means against the conditions which produce scurvy, and, moreover, how to treat the disease appropriately after it has once made its appearance, the *termination* has been much oftener *complete* or *incomplete recovery* than *death*. Experience has shown that the shorter the duration of the disease, the less fully developed its symptoms, and the sooner especially the patient comes under appropriate treatment, so much the greater is the prospect of *complete* restoration to health. The way in which the retrogression of the local symptoms and the restoration of the normal general condition take place in these mild cases, has been fully described in the section on the symptomatology. In a similar manner, only much more slowly, a gradual involution of all the morbid symptoms often enough takes place even in the more severe cases, and continues until all trace of the disease has disappeared, provided the requisite removal from the etiological influences has been accomplished before it was too late, and provided, moreover, nothing is neglected in the symptomatic treatment of the foci of disease. At other times, however, even under the circumstances just named, the recovery is *incomplete*, because local processes have been developed, while the scurvy was at its height, which are incapable of a complete resolution. Among these we may mention particularly, extensive loss of substance by ulceration of the gums, which under the most fortunate circumstances can only be replaced by a cicatricial

formation, or abnormal development of connective tissue in the inflamed and swollen mucous membrane, inducing a lasting thickening and induration of the gums; further, processes of a destructive nature in the skin, which leave cicatrices, or firm connective-tissue growths in the subcutaneous tissue, which often produce secondary atrophy of the muscles beneath, as well as false anchylosis of the neighboring articulations (especially the knee- and ankle-joints). Finally, among the cases of incomplete recovery belong also those which leave behind suppurative processes in the joints, or true anchylosis, or necrosis of the bones and cartilages, as well as those in which extensive adhesions form between the lungs and the pleura costalis, or the heart and the pericardium, as the results of a pleuritis or pericarditis scorbutica.

Death results in scurvy, as has been already mentioned, for the most part only after the disease has lasted for a long time, and when the localizations are numerous and severe. It is therefore usually the indirect result of an unabated persistence of the causes which give rise to the disease. The fatal result is in most cases directly due to a general functional exhaustion of all the vital organs, which is manifested by the signs of the most complete universal prostration. Less frequently the final catastrophe must be ascribed directly to some unusually severe, and at the same time, on account of their situation in vital organs, especially dangerous localizations or complications. Among the dangerous local affections should be mentioned particularly: hemorrhagic exudations into the pleural and the pericardial sacs, and the scorbutic affection of the large intestine, as malignant complications; on the other hand, we must mention especially the infectious form of dysentery and croupous pneumonia. Still another mode of *death* in scurvy is that by acute anæmia, or by bleeding. Death from this cause may occur at any stage of the disease, and may be due immediately, just as in other forms of the hemorrhagic diathesis, to excessive bleeding from cutaneous ulcers, or to an epistaxis which cannot be checked, or to hemorrhages from the stomach or to profuse losses of blood from the urinary passages and the genital organs. Although the number of cases of scurvy which end fatally in

this way is not very small, still this cause of death does not play so important a part in the general mortality of scurvy as it does, for instance, in that of hæmophilia or of morbus maculosus; it does not, therefore, deserve to be mentioned and counted as belonging in the first rank of the various modes in which the fatal issue has been observed to take place. Finally, we must also mention that, even during the earlier stages of the disease, and when, moreover, no special anatomical lesion of serious character exists, many scurvy patients have succumbed in an unexpectedly sudden manner to paralysis of the heart, with the symptoms of syncope. This has happened especially when the patients were obliged to make some violent movement, to stand up suddenly, etc. Hence, neither the extent nor the intensity of the demonstrable gross lesions can serve alone in every case as the measure of the degree of danger which is actually present. This depends also to a very great extent on the intensity of the general weakness, as well as on the occurrence or non-occurrence of external accidents which might occasion paralysis of the heart.

It is evident, from what has just been said, that the *prognosis* in scurvy is dependent upon very various circumstances. First and foremost, of course, it depends on the duration and severity of the case, the severity being estimated by the condition of the general strength of the patient, and by the site, the extent, and the intensity of the local processes; in the second place, on the possibility of procuring appropriate therapeutic aid and of placing the patient under the external conditions that are necessary for his recovery. Finally, even in mild cases that are progressing favorably, and in which all the dietetic and therapeutic measures necessary for the patient's recovery are being employed, we should always bear in mind the possibility of the occurrence of the dangerous accidents alluded to above, by which life may be very suddenly and unexpectedly jeopardized. A favorable prognosis should, therefore, never be too confidently given in advance, even where the circumstances appear in general propitious. The patient should at all events never be declared entirely out of danger until unmistakable signs of far advanced convalescence are given by the force and strength of the heart's

action, by the renewed vigor of the other organic functions, and finally by a nearly complete retrogression of all the local processes.

Treatment.

In speaking of the etiology of scurvy, and again in what immediately precedes, we have repeatedly referred to the great and blessed influence which wise and provident attention to certain sanitary needs in unusual seasons and circumstances, together with the adoption at the proper time of appropriate treatment, exert in limiting the development of this disease and in giving to its course a more favorable form. It may be boldly asserted, that in the whole province of special pathology there are few morbid processes in which a well directed *prophylaxis* and a strict compliance with the *indicatio causalis* are able to accomplish so much, as in the case of scurvy. It is true that our theoretical knowledge of the mode of origin of this affection, as well as of the manner in which the measures that are recommended in its treatment act, is at present deficient in many points ; but fortunately this hiatus does not seriously interfere with the success of the prophylactic and therapeutic measures. It is an historical fact that scurvy has become much less frequent, and has lost much of the malignancy which formerly distinguished it, since physicians learned to deduce, from the knowledge gained by experience in regard to its etiology, some evident conclusions as to practical methods of preventing and combating the dreaded evil.

The *prophylaxis of scurvy* includes, in the first place, like that of anæmia, a very large part of the domain of general, public, as well as private hygiene, since everything which tends to improve the outward conditions of existence of individuals, as regards their nourishment, habitations, clothing, employment, etc., and serves to elevate the physical condition of a population, not only increases in general their capital stock of health, but may be regarded at the same time as a special preventive of scurvy. Experience has abundantly proved that scurvy never was prevalent among persons whose outward conditions of exis-

tence at the time could be called normal ; this much is also certain, that the liability of an attack of scurvy is not particularly great in the case of any man who is free to satisfy his more important hygienic needs, and understands how to make a fitting use of this freedom ! It may, indeed, be safely asserted that any man is safe from scurvy who is able to command a sufficiently abundant and at the same time varied and nutritious diet, and plenty of good, pure, drinking water ; who has, moreover, the good fortune to possess a roomy, light, and dry dwelling, and can protect himself by proper clothing from the inclemencies of the weather, and who, finally, can preserve his mind in a quiet and cheerful frame, and is neither forced to overexertion of the body nor yet obliged to pass his life in complete physical inactivity, and that this immunity will persist so long as he continues in the unhindered possession and enjoyment of all these essential requisites to health. And as it is the positive duty of every sanitary board to secure these hygienic advantages for as many as possible and in the most thorough manner possible, it follows that the prophylaxis of scurvy necessarily coincides in *ordinary times and under ordinary circumstances* with general sanitary measures. The question of the prevention of scurvy assumes a more concrete form for the most part only under certain conditions of existence, which may all be considered as *exceptional* in their nature, and therefore, from the standpoint of strict hygiene, as *anomalous*. Let us therefore, without further digression, enter at once upon the consideration of these somewhat less usual conditions of physical existence, which are well known to involve for certain reasons an outward predisposition to scurvy, and let us briefly discuss, as an addition to what has been previously said under the heads of the history and etiology of scurvy, the most important of the things that can be stated and recommended as of proved value, in regard to the prophylaxis of scurvy under such circumstances.

Here again our attention is naturally first called to the occurrence of this affection *on shipboard*, and we must consider by what precautions its breaking out at sea can be most surely prevented. Since the great liability to contract scurvy on a voyage in former

times was undoubtedly due to the sort of provisions with which ships were then supplied, and since, moreover, in recent times the disease has scarcely ever appeared on shipboard until after the fresh meat, the green vegetables, and finally, the store of potatoes, had been gradually exhausted, and the crew had been confined for a considerable period to the so-called "sea-food," the prophylaxis of the disease evidently consists first of all in supplying ships, before sailing, with an abundant provision of good potatoes, which are the most easily procured and preserved of all the antiscorbutic aliments. It is no less advisable to replenish the store of potatoes as often as necessary at intermediate stations, so as to prevent, if possible, any scarcity of this article of food in the daily ration of the sailors. The preservation of large quantities of green vegetables (in hermetically sealed cans, etc.) is, of course, much more difficult and especially much more expensive, and the regular distribution of this sort of food to the whole ship's company would hardly be practicable as a permanent thing, particularly on board of merchant vessels. It is hardly necessary to say that, whenever by a fortunate combination of circumstances it is possible to obtain fresh vegetables during a voyage, the opportunity should never be neglected; the crew should be encouraged to indulge freely in them at the time, and a supply should also be laid in for future use. For reasons that are easy to understand, the renewal of a ship's supplies of green vegetables becomes a matter of the greatest difficulty in the case of voyages to the barren polar regions and of lengthened sojourn there. A few moderately palatable, nutritious plants, such as the *spoonwort* (Cochlearia officinalis), the common sorrel (rumex acetosella), the dandelion (taraxacum officinale), the house-leek (sedum acre), and some other species are, however, found among the scanty vegetation of those regions, and when the voyage falls in the short polar summer, the men should be encouraged to gather these plants and to use them as vegetables or salads. We venture to doubt whether the spoonwort, so much vaunted in former times, and even yet, as a prophylactic against threatened and a specific for existing scurvy, really possesses any "very special" antiscorbutic powers, and do not believe that this power, if it exists, resides in the sulphuretted ethereal oil of this

cruciferous plant. We are disposed rather to account for the important and gratifying rôle which spoonwort has unquestionably played in the history of the prophylaxis as well as of the treatment of scurvy, simply by the circumstances that the region of distribution of this plant extends unusually far to the north, and that mariners in the higher latitudes, when seeking for vegetable food on the barren strips of coast of the arctic regions, very frequently found this spoonwort and often nothing else.

The plant is found, according to Mertens, Egede, and others, in incredible quantities on the coasts of the extreme north (Spitzbergen, Greenland). It thrives even in sand or on almost naked cliffs, wherever even minute quantities of the droppings of birds or the excrement of seals have fallen. Its taste is said to be in the polar regions less pungent, but more of a bitter-sweet (Krebel). The dandelion (taraxacum officinale), which is so common on our grass-lands, and affords a savory vegetable especially adapted for use as a salad, is also met with by the polar explorers in the very farthest north. It doubtless owes its great reputation as a prophylactic against scurvy principally to this accidental circumstance.

We stated, while speaking of the etiology, that bread, dried leguminous vegetables, and rice, although all vegetable aliments, still do not possess the antiscorbutic properties of potatoes and green vegetables. *Sauerkraut*, however, would seem to be a good and very efficient substitute for these latter in the alimentation of the sailor; of its efficacy in preventing the scurvy, Lind, Mertens, and other earlier writers were thoroughly convinced. Lind, in particular, stated that on board of Dutch ships, which were habitually well supplied with sauerkraut, scurvy was unusually rare, and he recommended most urgently that ships should take with them large supplies of this aliment, which, when packed in casks, can be preserved in good condition for years. That this advice of Lind's was really well grounded seems evident from the fact that at the present day English and other marine surgeons always recommend an abundant supply of sauerkraut as well as of potatoes, on sea-going vessels, as one of the principal prophylactic measures to be taken for the prevention of the scurvy. It seems worthy of mention in a theoretical point of view, that sauerkraut, as usually prepared, loses nothing of the nutritive elements of the fresh cabbage (especially

of its nutritive salts), so that it may in fact be looked upon as a complete, though not a very easily digestible, substitute for the fresh vegetable substance. Finally, let us once more recall to memory the fact, of ethnological interest, that certain peoples (Laps and Finns) dwelling in the far north are able during the long winters to protect themselves successfully from scurvy by the daily use of a substance similar to sauerkraut—namely, common sorrel, gathered in the autumn and prepared with reindeer's milk. They consume considerable quantities of this substance with the flesh of animals killed in the chase. Other northern peoples who live exclusively on meat,—for instance, the Quaens and Normans,—suffer severely from scurvy.

Of other articles of food, *juicy fruit* certainly approaches most nearly to vegetables in its chemical properties, and like them it is also valuable as a preventive of scurvy. As *oranges* and *lemons* are, of all kinds of juicy fruits, the easiest to pack away and to keep in good condition on shipboard, it has become a pretty general custom in recent times to lay in supplies of them on extended voyages, and to deal them out to the crew at intervals, in order to diminish the danger of an epidemic of sea-scurvy. The so-called *lemon-juice* is also employed as a prophylactic against scurvy, in the British and some other navies. It consists of the expressed juice of lemons, clarified, and for its better preservation mixed with brandy in the proportion of 10:1. On every long sea-voyage, even at the present day, each English seaman receives daily, after the first fortnight, 30 grammes (℥ i.) of lemon-juice and 45 grammes (℥ iss.) of sugar as an antiscorbutic ration. As, however, the lemon-juice, even when prepared as above described, did not always remain good for sufficiently long periods, and as, moreover, in spite of its regular employment, scurvy sometimes broke out on shipboard, it was subsequently discarded in the Austrian navy, where it had been employed for a time (Duchek). It has also lost much of the favor with which it was temporarily regarded by the naval authorities of several other nations. But, in our judgment, it is not fair to conclude that a preservative is totally useless because it is not *entirely* sure, or does not protect in *every* case; and

there is as little justification for the belief that all necessary prophylactic precautions have been taken against scurvy by the distribution of any one *other* article of diet alone. The continued employment of lemon-juice on the ships of the first maritime power of the world—namely, of England, cannot, as it seems to us personally, be ascribed to a mere conservative whim; on the contrary, it furnishes noteworthy extrinsic evidence that lemon-juice must possess certain antiscorbutic virtues, when employed in connection with a sea-regimen in other respects rational. It must not by any means be imagined, however, as Chalvet very justly observes, that the use of plain citric acid in the form of lemonade, or of lemonades prepared with other vegetable acids, can in any way take the place, as prophylactics, of lemon-juice or of the juice of other acid fruits; or that, for instance, in order to prevent scurvy on sea-voyages, it is only necessary to carry a large supply of crystallized citric acid, which is very easily preserved. According to the statements made in another place, it is in the highest degree improbable that the pure vegetable acids possess any efficacy whatever as direct antiscorbutic agents; on the contrary, there is good reason to believe that it is only when in the form of their unstable combinations with potassa (precisely the form in which they are chiefly contained in fruits and in many vegetables) that they possess these antiscorbutic qualities. Hence, the fact that vegetable acids, given alone, are worthless both as prophylactic and as therapeutic agents in scurvy (Beckler, Duchek, and others), does not prove anything whatever against the efficacy of the expressed juices of fruits.

Of animal food, apart from fresh meat, which should be procured as often as possible when opportunity offers, and the fresh milk of stalled animals (cows), supposing that such live tenants can be accommodated on shipboard, *canned meats* and *condensed milk* are to be recommended above all other articles as prophylactics against sea-scurvy. As further substitutes for fresh meat, which at all events are far preferable for sea-diet to the justly decried salt junk, the following might be mentioned: the so-called meat-biscuit, meat-powder, meat preserved in honey casks, or enveloped in sugar, and also meat which has been suit-

ably prepared for preservation by immersion for a short time in creosote water. We refer the reader to Krebel[1] for further information as to the modes of preserving and cooking these various preparations of meat, all of which, though not in an equal degree, deserve to be recommended as supplies for a sea-voyage. *Liebig's Extract of Meat* is also to be highly recommended. This preparation, although entirely lacking in albumen, contains otherwise in the greatest abundance and in condensed form precisely those substances (salts of potassa) which the meat loses most during the process of pickling, and to the want of which modern writers are disposed, not without good reason, to ascribe the frequent occurrence of scurvy after long-continued and exclusive use of salted meat. The history of this disease furnishes numerous examples from former times which seem to support this theory.

In the hygienic administration of a ship, the most careful attention must be paid to the *condition* of the food used, as well as to the choice of the diet, if it is desired to render the protection against scurvy as certain as possible. Spoiled articles of food, whether they be meat, biscuit, or anything else, not only prove decidedly injurious to health by provoking more or less serious derangements of the digestion, but it would also seem that the development of many epidemics of scurvy must be ascribed to the use of such articles in the sea-diet. It is the duty, therefore, of those charged with the supervision of the daily rations of the crew, not only to see that the food used is sufficient in quantity and properly prepared, but also that it is in a good state of preservation; whatever is suspicious in this latter respect should be promptly discarded, and, if any intermediate stations are made, the deteriorated articles should be replaced by a new supply in the best possible condition.

Good drinking-water is also a very important preservative against scurvy at sea. Supplies of drinking-water on shipboard can with a little care be kept from spoiling for a long time; they should be contained in large, tightly closed, iron tanks, placed in the coolest possible part of the ship. There are, moreover,

[1] l. c. S. 232–237.

various methods of more or less value by which foul drinking-water can be purified, either by filtration, or by precipitation of the dirty slime that has formed in it, as well as methods by which drinking-water can be obtained by the distillation of sea-water. The necessary information on these points will be found in Krebel's[1] work. Finally, as often as a fitting opportunity presents itself, the store of drinking-water should be renewed, a freshly drawn supply of good spring-water being taken in. This is a duty which must be fulfilled with as much care as the replenishing of the supply of provisions.

As other beverages to which we are entitled, by abundant experience, to ascribe a protective efficacy against scurvy, and the daily use of which on protracted voyages is, therefore, desirable, we may mention especially *tea*, good *beer*, particularly the *spruce beer* (Sprossenbier), prepared by adding turiones pini s. abietis to the fermenting mash, or essence of spruce to the fermented drink ; and finally, *wine*, or, in place of it, *cider*. The value of all these beverages, as prophylactic agents against scurvy, may be considered as thoroughly proved by the decrease in the frequency of this disease at sea since they have been generally introduced into the diet lists of ships ; and it is a very striking fact, that, like the antiscorbutic aliments (green vegetables, fruits, etc.), they all are remarkable for the large amount of potassa which they contain in combination with carbonic acid and vegetable acids. This circumstance furnishes still another argument in favor of Garrod's theory, that the occurrence of scurvy is due to an insufficient supply of potassa to the organism.

However, the etiology of scurvy does not exclusively or in all cases consist in a faulty supply of food and drink ; and as numerous observations prove that epidemics of the disease can occur on shipboard even when the supply of food and drink is most perfect, it is evident that they must be referred to *other* injurious causes. Hence, the prophylactic measures to be taken against scurvy at sea should not be limited merely to an appropriate regulation and supervision of the alimentation. It

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[1] l. c. p. 240–245.

is also essential that strict attention should be paid to all those other injurious influences by which a prolonged confinement on shipboard may be rendered dangerous in this respect. Some of these influences are merely auxiliary, but others are perhaps of cardinal importance. Among them we must mention, in particular, defective ventilation and uncleanliness of the ship, frequent exposure to wet and cold, with the consequent drenching and chilling of the body, excessive hardships, and depression of spirits. Every effort must, therefore, be made to secure under all circumstances the greatest possible *cleanliness*, so far as this is practicable on board of a ship on a long voyage. Special attention must also be paid to the *proper ventilation* of the covered spaces in the ship, since a stagnation of air vitiated by all sorts of gaseous emanations in these spaces, seems plainly to have had a direct causative connection with the outbreak of many epidemics of scurvy on shipboard. For this reason alone, apart from the other advantages of good, pure air, it is especially advisable, whenever the temperature of the air and the state of the sea will permit, to open daily the ports of the ship and the cabin windows, so as to secure a free exchange of air. It is of course a very great advantage to have the air in the interior of the ship renewed also during stormy, cold, and damp weather, and for this end various ventilating apparatuses have been proposed and employed, by means of which, without opening the windows of the ship, the air can be changed as often as necessary.[1] The first apparatuses of this sort were introduced by Baskoweṅ and Ventura.

The *clothing* of the crew is another matter which deserves attention. It should be appropriate for the climate, but in particular should be of such a kind as to protect the body as far as possible from chill and wet. A sufficient supply of woollen shirts and drawers should be in the possession of each man, especially on voyages in the northern seas; in addition, thick outer garments. In regulating the often very exhausting duties of the *ship's service*, the attempt should be made to distribute by regular reliefs the burden of the general work in such a

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[1] *Krebel*, l. c. p. 227.

way that it may bear as equally as possible upon the shoulders of all, and that rest and exertion may succeed each other at suitable intervals. At the same time, however, the individual's capabilities should be kept in mind as far as possible, and the tasks allotted to the weaker and more delicate members of the crew should not, when it can be avoided, be as severe as those allotted to the stronger and more robust. It must, moreover, always be borne in mind, that notwithstanding a fair distribution of the burden of duty, in which the weaker individuals are favored in some degree, the amount of bodily exertion unconditionally demanded from each one varies very greatly under different circumstances (for instance, it is much greater when the weather is stormy and the sea high than in calm weather), and that the supply of food, as well as of exhilarating drinks, should be in proportion to the greatness of the exertions called for. Nothing can in fact be more detrimental to the physical well-being of a crew, and more favorable to the development of an outbreak of scurvy among them, than a too rigid adherence to formal regulations which prescribe a uniform and almost unvarying sea-diet, both as regards food and drink, without reference either to the different needs of differently constituted men, or to the great variations in the severity of the bodily exertions demanded. There is no other situation in which a certain fluctuation in the amount of the day's rations, gauged on an intelligent knowledge of physiological principles, is as desirable, and in a prophylactic point of view as advantageous, as it is on shipboard. Finally, it is also without doubt the duty of those in command, in the trying times and precarious situations which are so often met with on long voyages, to exert to the utmost their moral energy, and to bring into play their intellectual endowments, in order to maintain or reawaken courage, endurance, good humor, and a hopeful state of mind in those under their control. The very beneficial influence of these *psychical* factors on the health of the crew has been repeatedly and with good reason insisted upon, and from the earliest times they have been considered as specially efficacious in warding off the attacks of scurvy. The preceding remarks can only be looked upon as a very general and incomplete outline of the precautions

that must be taken by the officers charged with the superintendence of the ship's hygiene, in order to guard as far as possible against an outbreak of scurvy—that formerly so dangerous and even at the present time so threatening enemy of the sailor. For further details in regard to prophylactic measures, we must refer to the works which treat specially of this subject, in particular to Krebel's monograph. We shall only add, in addition to what has already been stated, that in many cases unexpected occurrences will make it necessary to abandon for a time some one or more of the elements of the prophylaxis, but that naturally the possibility—indeed, the probability of an outbreak of scurvy then increases in a corresponding measure, and eventually perhaps the disease actually makes its appearance. Hence, sea-scurvy, as a topological variety of the disease, does not as yet belong entirely in the domain of history. In addition to the question of its prevention, that of its treatment will in all probability long continue to occupy the attention of naval authorities and ships' surgeons.

The prophylaxis of the so-called *land-scurvy*, or, more correctly speaking, of this disease when occurring on land, for in its nature it is entirely identical with sea-scurvy, falls principally in the domain of military hygiene. The reason for this is, that this variety of the disease, as history proves, has occurred both in ancient and recent times with special frequency and destructiveness in besieged cities, as well as during long marches and military operations performed under circumstances of unusual difficulty—in short, as a result of the incidents of war. The measures to be adopted for the prevention of scurvy in time of war should be dictated, in the first place, by a prudent foresight in regard to the possibility of towns being besieged. With this possibility in view, these measures should consist principally in provisioning as abundantly as possible all fortified places, particularly with sufficient supplies of those easily preserved aliments and drinks—for instance, potatoes, sauerkraut, condensed milk, and wine—which possess unusual antiscorbutic efficacy; secondly, in securing a sufficient number of cattle and horses, with the necessary quantity of dry fodder (oats, hay, etc.), in order that the besieged garrison and the civil population may

have fresh meat to eat as long as possible; thirdly, in a strict examination and repeated inspection of all springs and permanent sources of water-supply in the fortified place, in order to prevent contamination of the drinking-water by filth or effluvia; finally, when the place is really besieged, in a regulated distribution of food and drink to the troops, comprising the garrison and the inhabitants, in relieving at proper intervals the troops who are charged more specially with the duty of defence, and last, but not least, in the employment of the moral influence of the commanding officers for the encouragement of the defenders and of the citizens as soon as any abatement is noticed of the heroism manifested at the beginning. It cannot, however, be denied that, even with the help of all the material as well as mental and moral forces, it is not always possible to prevent permanently the outbreak of scurvy in a besieged town, and that the prophylaxis of the disease, in this field of its special predilection, will constantly encounter difficulties, if possible, still greater than in the field of maritime expeditions. It nevertheless forms a most important part of the duty of all prudent strategists to meet this powerful ally of the enemy by the most energetic employment of all available forces, and by the most intelligent foresight in the directions that have been pointed out. We need not insist on the necessity of supplying troops operating in the field, more particularly during a winter campaign, with sufficient stores, which should be supplemented by additional supplies of food, wine, warm clothing, etc., sent to the soldiers from their homes. The great facilities of communication in modern times render the proper maintenance of troops, at least while operating in civilized countries, much more feasible at the present day than formerly. It is probable that to this external circumstance is due in no slight degree the fact that scurvy has been so much less frequent during the great wars of the latest times, during which, apart from its occasional prevalence in besieged fortresses, it has only showed itself in very rare instances among bodies of troops operating in the open field.

In order to guard against the possible occurrence of scurvy as a *pestilence in prisons*, or as a local epidemic in *alms-houses*, *foundling asylums*, *barracks*, etc., it is of the first importance

that the food provided for the inmates should be sufficiently abundant and not too monotonous, and particularly that it should not too exclusively consist of bread and dried leguminous vegetables; a constant and abundant supply of good, clear drinking-water should also be furnished. In the next place, we must recommend, as of hardly less importance than a proper supply of food and drink, a careful attention to cleanliness, and particularly to the proper ventilation of the cells and inhabited rooms. Finally, a certain, not too limited amount of exercise in the open air, is of the utmost advantage, especially in the case of prisoners who would otherwise be forced to pass the whole day in sedentary occupations in their place of confinement. Without this exercise the body is liable to become prematurely infirm, and thus more predisposed to attacks of scurvy. When, on the other hand, prisoners are required to perform, for any length of time, work demanding much greater exertion of bodily strength than they are accustomed to—for instance, in erecting buildings, agricultural labors, etc., the hours of labor should not be excessive; and in proportion to the labor required, the ration should be improved by the addition of meat, green vegetables and potatoes, as well as milk and beer or wine. Experience has sufficiently proved that the neglect of these measures, under such circumstances, has relatively often been followed by outbreaks of scurvy among prisoners. Finally, we would further observe that, whenever it is necessary to build a prison, hospital, alms-house, barrack, or any other building destined to serve as a place of more or less compulsory abode for large numbers of human beings, the very greatest possible attention should, as a matter of course, be paid to the dryness and roominess of the localities to be occupied by the future inmates. Care should also be taken to secure a good location for the proposed establishment, both as regards the nature of the subsoil and the facilities offered for the free admittance of light and air—in short, everything should be attended to in the execution of the plan, which can in any way tend to increase the salubrity of the institution.

Lastly, the prophylaxis of scurvy demands also that, in years in which, owing to bad crops, especially of potatoes, a *pandemic*

spread of scurvy among the poorer classes of any country is threatened, public charity and even direct government help should come forward and make up for the failure of the crops by procuring the necessary supplies of vegetable food from other countries; also that private and public assistance must do their utmost to alleviate any other material misery, whatever it may be, that threatens at any time to undermine the general health of the people. For, although all kinds of external privations may not lead with equal readiness to the development of an epidemic of scurvy, still all do, indirectly at least, contribute to its production, since they all lessen the power of the organism to resist disease, and thus, by preparing the ground, enable the real causes of scurvy to exert their noxious influence more potently.

The medical experience of the present century has taught, at times in the most distinct manner, that a comprehensive and at the same time energetic administration of the hygienic principles which have just been described, raises an exceedingly strong barrier against the development of scurvy, both at sea and on land. In the first place, epidemics of scurvy of such intensity and extent as were formerly of frequent occurrence, have been very rare of late years. Moreover, whenever, either from simple neglect or from necessity, one or other of the more important of the precautions mentioned has been left unattended to, and, in consequence of the omission, an epidemic of scurvy has broken out, the subsequent elimination at the earliest possible moment of the offence against sanitary laws has almost always proved to be a sure and unfailing means of preventing the further extension of the pestilence. It has also been proved by numerous observations, that these hygienic measures exert not only a prophylactic, but also a very important directly *curative* action, since they constitute, when carried out with great strictness and properly adapted to the etiology of each individual case, the groundwork of the causal treatment. We have already repeatedly stated that, in addition, a rational prophylaxis, a strict compliance with the *indicatio causalis*, of which we shall presently speak, has proved itself to be not merely in some degree, but indeed in the highest degree, effective. It is, therefore, sufficient for the present to call to mind once more,

that a rapid change for the better takes place invariably in mild cases, and with striking frequency even in the severest cases of this disease, as soon as the treatment succeeds in doing away with the exciting causes of the disease.

But the thorough fulfilment of the indicatio causalis presupposes in the first place an actual *knowledge* of the causes of the disease, in concreto; a mere theoretical acquaintance with the injurious influences, which may in general give rise to scurvy, is not sufficient. Hence, an accurate etiological investigation is essential for a rational and successful treatment in individual cases as well as in individual epidemics of scurvy. This examination must determine the special causative factors that have been active in each case, and make them serve as a basis for the plan of treatment to be adopted. It will not do to enter upon the causal treatment of scurvy with any preconceived ideas as to the exclusive agency of some one or other exciting cause, nor to base the treatment, wherever an epidemic of scurvy prevails, always on the same etiological plan; on the contrary, it must be constantly borne in mind that not even the pathogenesis, much less the etiology of scurvy, can be said to be uniform. Even though, for instance, one particular peccant circumstance—namely, *the deprivation of fresh vegetable food*, seems to have played with *common frequency* the part of the exciting cause, and although the *very numerous* cases and epidemics of scurvy thus produced can be cured more rapidly and surely by immediately supplying the aliments of which the patients have been deprived, than by any other means; still, it would be very absurd to regard salad, green vegetables, and potatoes on this account as a *universal* remedy for scurvy. On the contrary, the history of the disease contains many examples which prove that epidemics may also at times arise, spread, and attain great proportions even when the supply of fresh vegetables is perfectly sufficient, and that, as we may at once add here, the *curative* efficacy of the articles of food mentioned, although undoubted in very many, is by no means evident in *all* epidemics and isolated cases. Wherever the scurvy is to be attributed in concreto to the influence of *other* causes, the fulfilment of the indicatio causalis demands, *a priori*, other therapeutic measures, and experi-

ence has shown, moreover, that such other modes of treatment are often much more efficacious than an increase in the supply of juicy vegetables. This is particularly true, in regard to the treatment to be employed in all those epidemics, the etiology of which points to unhealthy conditions of the habitations occupied by those attacked rather than to defects on the part of the alimentation. In such cases it has been many times demonstrated, that a transfer of the patients to more healthy (lighter and dryer) habitations proves a means of cure as much to be relied upon as the change to a correct diet in those, much more numerous, cases, in which the disease is due to improper or insufficient food.

A very instructive instance of this is to be found in the rapid improvement and recovery of all the scurvy patients of the low-lying and damp military hospital at Givet (1847), as soon as they were transferred to a neighboring height, although no other treatment was adopted.

We cannot spare time here to enter again into the details of the measures required to carry out the indicatio causalis in each particular case. We must refer to the full statements given under the head of Etiology, for an account of the prejudicial influences, the elimination of which may be desirable in the individual cases, and to those given under the head of Prophylaxis, for an account of the measures to be adopted.

It seems to us very doubtful whether there is or ever can be any *essential* mode of treatment for scurvy apart from the causal treatment, the success of which, however, when properly individualized and sufficiently energetic, is exceedingly gratifying. It is true, that the search after such a mode of treatment has seriously occupied the attention of physicians, especially in former times, and that many different remedies and methods of treatment have at various times, some even quite recently, been claimed to possess specific antiscorbutic efficacy. If, however, we admit that neither the etiology nor the pathogenesis of scurvy is the same in every case, and in our opinion this view is the only one that accords with the present state of medical knowledge—or if, to express it in other words, we feel ourselves forced to admit that the collective symptoms of scurvy, identical in a clinical point of view, may in different instances be engendered by

different external influences and in *different ways*, we must naturally define and limit more closely the conception of an "essential" mode of treatment for the disease. The remedy namely, which is to fulfil the indicatio morbi, must be able to exert a decidedly favorable and curative action on the peculiar general cachexia, and the hemorrhagic-inflammatory local symptoms in all the *etiologically different* forms of the disease; in other words, *independently of the particular mode of development of the individual case or epidemic.*

Such an "antiscorbuticum," the radical, therapeutic action of which on scurvy should be about analogous to the action of iron in the treatment of anæmia due to different causes, is, however, as yet wanting in our treasury of remedies, and is, therefore, still to be found. Instead of it we find mentioned in the history of the treatment of scurvy, apart from the noted very efficacious dietetic directions already described, which serve both for the general prophylaxis of the disease, and the special fulfilment of the indicatio causalis in the individual cases and epidemics, only such remedies as either 1), really belong, or at least appear to belong, to a *more comprehensive causal treatment*, or 2), merely comply with the *indicatio symptomatica.* To the first category belongs, for instance, the often recommended, and also often successful, employment of the *fresh juices expressed* from the leaves, roots, and fruit of different plants, such as the different varieties of the brassica and nasturtium, the taraxacum, cochlearia, sedum acre and sedum telephium, chelidonium, beccabunga, oxalis, and different varieties of rumex—also beets, turnips, carrots, radishes and horse-radish, cherries, currants, lemons, barberries, whortleberries, the fruit of the cornel tree, etc. The administration of these juices, however, is plainly nothing more than the administration of the alimentary substances themselves in a more *medicinal* form, and the same results will be attained in as certain and thorough a manner by the use of fresh vegetables, salad, and fruit, as articles of diet. The treatment by the juices, moreover, in its nature and its effects is principally a mere compliance with the indicatio causalis in the far greater majority of cases of scurvy. If it is desired to make a therapeutic use of these juices, in severe cases

of the disease, in order to increase the effect of a corresponding diet, they should be given in quantities of from 60,0–120,0 grammes (℥ ij.–jv.) daily, or, if the case requires it, in still larger quantities. On the theoretical presupposition that it is the *organic acids* contained in many of the plants mentioned which constitute their curative principle, these acids themselves were recommended as antiscorbutic "remedies." Experiments in the treatment of scurvy patients were accordingly made with tartaric acid, citric acid, and at times with other organic acids; the result of which, however, was on the whole so completely negative that the theory on which they were based was soon demolished. In regard to the presumably active principle of these vegetable substances, namely, the potassa, it is to be regretted that no sufficiently extended and exact series of experiments have as yet been made to determine the therapeutic action of the *pure vegetable salts of potassa* (bitartrate, citrate, and acetate of potassa). However, Brouardel, on the ground of his own experience during the last Paris epidemic, at all events commends the abundant use of *boiled wine*, which in the process of boiling has lost part of its alcohol and water, and for this very reason contains the *bitartrate of potassa* in more concentrated form. He also recommends, as do likewise Bucquoy and others, the administration of the tartrate of iron and potassa. Certain *inorganic* combinations of potassa, in particular *nitrate of potassa*, dissolved in vinegar (Cameron) or in water (Henderson), and given in doses of from 8,0–15,0 grammes (ʒ j.–ij.) daily, have also been strongly advocated in former times, as well as quite recently (Pechey). But even if future experience should establish still more firmly and surely the truth of the maxim, that, as a want of potassa in the food is a frequent cause of scurvy, so the salts of potassa, especially those which are most easily disintegrated and assimilated, possess a decided therapeutic action on the disease, we shall still be compelled to ascribe this favorable action to a compliance with the indicatio causalis, and not with the indicatio morbi. In other words, the employment of them as medicaments compensates for the previous deprivation of food, rich in potassa, and eventually arrests the morbid process occasioned by this deprivation. Finally, in the class of remedial

agents which probably owe their efficacy to the potassa they contain, we may also count *the barm of beer*, which has been so largely and at times so successfully employed in the treatment of scurvy. The credit of first introducing this substance as a remedy belongs to Neumann,[1] who found yeast wonderfully effective in the treatment of this disease in all its stages, and recommended its administration internally, in doses of from 180,0–300,0 grammes (℥ vjss.–jxss.) daily. Neumann's favorable opinion has been shared by a great number of physicians and authors (among others G. S. v. Himmelstiern, Windisch, Fink, F. v. Niemeyer, and more recently Doering), while others again, among whom are Krebel, and particularly Duchek, although they do not deny entirely the usefulness of this substance, rate it, however, in general much lower than Neumann does. If we keep in mind the fact that barm, being a vegetable organism in a state of very active proliferation, is, like all rapidly growing parts of plants, very rich in potassa, we must admit that its so highly lauded antiscorbutic efficacy appears to be a significant illustration of Garrod's theory; at the same time this richness in potassa, when considered in connection with the favorable results obtained by the use of fresh vegetable food in so many cases of scurvy, explains, to some extent, the efficacy of barm. Finally, it ought not to be a matter of surprise that a remedy usually so valuable should have proved on the whole of so little efficacy in cases of scurvy, which were notoriously not due to any want of food containing potassa in sufficient abundance (potatoes). The cases observed and treated by Duchek were precisely of this character.

Let us now turn to those other therapeutic substances which, in our opinion at least, possess only a symptomatic value. Among these we must mention in the first rank the various preparations of *quinine*, the *pure bitters* (gentiana), *the aromatic bitters* (calamus, cortex aurant.) and the aromatics (rad. angelicæ, rhiz. zingiberis, cortex cinnamomii). It does not seem to us possible that these substances, the beneficial influence of which, on the condition of patients, we are by no means disposed to

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[1] Hufeland's Journal. Februar 1832.

deny, can exert in cases of scurvy any other than the ordinary tonic and digestive action which they are wont to display in so many other cachectic conditions, and wherever in general there is prostration of the digestive powers. The same is, in our opinion, also true of the tonics, in the more limited sense of the word, namely, of the preparations of *iron*, which are said to be very useful, especially in severe cases, or when convalescence is retarded. If we bear in mind that the scorbutic cachexia in its more developed forms leads to pronounced anæmia, and especially oligocythæmia, or, to put it in other words, is very usually complicated with this latter anomaly, it will be evident that the favorable effect of iron in some cases is a proof, not that the remedy possesses any actual anti-scorbutic property, but simply that it has been indicated by the *symptoms* in the concrete cases. About the same may be said, too, in regard to the actual or pretended cures said to have been obtained by the use of the *mineral acids* (Cooper, and others), particularly sulphuric and nitric acids, or of the *ergot of rye* (Canuto Canuti, Henoch, Bauer, and others), and of *the chloride of iron* (Bouchet, Bourdon). All these medicaments, on account of their more or less proved powers as *hæmostatics*, were employed tentatively in the milder as well as the more severe cases, against the hemorrhagic diathesis; they were prescribed as in other diseases with a specific object.

It is a notable fact, however, that most of the medicaments in question were, on the whole, of no great service in combating the hemorrhagic accidents in scorbutics, at least when given internally. Further than this they did not usually exert any essential influence on the scorbutic cachexia, the eradication of which is of primary necessity, since it constitutes the basis on which the hemorrhagic processes, as *symptoms* of the general disorder, are developed. In any case, therefore, these medicaments, according to their action must, like the tonics and digestives, be classed simply as symptomatic remedies.

Finally, it still remains for us to discuss very briefly those measures which are to be adopted in the symptomatic treatment of scurvy, and which are directed *particularly against the more serious individual symptoms.* Of all the symptoms of

the disease, the *functional weakness of the muscular apparatus*, and particularly of the *heart*, which is so intense in the severe cases, is by far the most dangerous, and hence demands the greatest amount of attention in the treatment. The treatment of this symptom must be both *negative* and *positive.* On the one hand, the greatest pains must be taken to avoid whatever might still further enfeeble the patient in his already prostrated condition, while, on the other hand, everything possible must be done to raise him up from this state. In the first place, all directly enfeebling treatment and medication must be avoided, particularly any *unnecessary limiting of the supply of food*, or the *administration of the more powerful drastics* when constipation happens to exist, or *the employment of an active mercurial treatment* to combat inflammatory localizations or complications (pleuritis, pericarditis, enteritis scorbutica, etc.), or more especially *local* and *general blood-letting.* With regard to the use of purgatives, we must mention explicitly that the more active among them (senna, jalap, aloes, colocynth, etc.), not only exert an enfeebling and prostrating action, but in scorbutics readily excite violent hemorrhages from the bowels, which cannot be checked. Hence, whenever in such patients constipation renders the employment of some therapeutic means desirable, an endeavor should be made to evacuate the bowels by the use of clysters, or at most only by the administration of very mild laxatives (castor oil, tamarind pulp, bitartrate of potassa). The employment of mercurials is also forbidden, even when in the concrete case they might seem specially indicated for some other reason, for experience has shown that these preparations, in addition to their injurious action upon the general nutrition, almost always exert, after a short interval, an exceedingly unfavorable influence on the scorbutic affection of the gums, and moreover, usually aggravate the hemorrhagic diathesis. Finally, the direct abstraction of blood by leeches or by the lancet, although it has been occasionally recommended as a means of combating the scorbutic dyscrasia (Opitz), is still in general, and very justly, too, looked upon as absolutely counterindicated in this disease, because of the prostration which it produces. At the utmost it might be allowable as an occasional expedient in those very pe-

culiar and unusual cases where there is a marked disproportion between the quantity of the blood—that is, the burden to be set in motion by the heart, and the momentary capability of the heart muscle to perform this task—or, to state the case more precisely, when extreme and dangerous cyanosis occurs in the course of a still recent attack of scurvy in a previously strong and full-blooded individual. Under these exceptional circumstances, the abstraction of a moderate quantity of blood by the lancet, or the application of a number of leeches over the left border of the sternum near the heart, may perhaps, sometimes, actually save life, since by a partial depletion of the venous system the physiological task of the heart will be temporarily diminished. Under all other circumstances, however, the physician must carefully shun these measures which would only aggravate the scorbutic disturbance by the addition of anæmia as a complication ; on the contrary, every pains must be taken to preserve the stock of blood as intact as possible.

There is still another condition in which the treatment of the weakness of the heart in scorbutics must be rather of a negative or prohibitive character. Whenever, namely, the disease is far advanced and the feebleness extreme, the patient must be prevented, as far as possible, from making any movement of the body, and should constantly be obliged to retain a nearly horizontal posture in bed. The reasonableness of these precautions must be plain to all. The latter, in fact, is indicated not only in the functional adynamia occurring in the course of scurvy, but in all other adynamic conditions as well, and perhaps the only reason why it requires special mention in the symptomatic treatment of scurvy is, that in this disease a relatively large number of sudden deaths have been observed, which were due to the imprudence of the patients in sitting up, or standing up and walking about too soon. Finally, the *positive* measures which must be employed to counteract the feebleness of the heart and the general functional adynamia, do not differ from those which are usually adopted in analogous cases. The use of *nourishing food*, which must be, however, *easily digestible*, and appropriate to the weakened digestive powers, is especially to be recommended, as well as the diligent administration *of analeptics*,

especially of strong wine, cognac, or, if this be unattainable, of other alcoholic stimulants, and finally also of camphor and other direct stimulants, whenever paralysis of the heart is threatened. The administration of the preparations of iron and quinine, of which we have already spoken, is also generally very useful in the later stages of the disease. Lastly, a trip to the country, and the use of cold baths and similar *invigorating* measures are to be recommended during reconvalescence, to eradicate the last traces of weakness.

Among the local symptoms of scurvy, the *affection of the gums* in particular frequently calls for special *local* treatment. In combating this symptom, in addition to cleanliness and frequent rinsing out of the mouth with cold water or with water and vinegar, the local employment of astringents is to be recommended. In many cases great benefit has been derived from painting the loosened, suffused, and inflamed gums with a solution of nitrate of silver, alum or tannin, with the tincture of catechu or ratanhia, or with a decoction of Peruvian oak or willow bark; also from frequently touching the easily bleeding, superficial losses of substance, as well as the deeper ulcerations, with a solid stick of lunar caustic. Tincture of myrrh, spirits of cochlearia, borax, and chlorate of potassa have also not infrequently been employed, locally, with good results in scorbutic stomatitis, and may therefore be briefly enumerated here in connection with the remedies just mentioned, as well as finally the mineral acids, in a sufficiently diluted form; for instance, hydrochloric acid (Cejka) in the form of an ointment, etc. It should also be recalled to memory here, that in many cases even the more intense forms of the scorbutic affection of the mouth have disappeared in a very short space of time, without any direct local treatment, but simply under the favorable influence of an appropriate treatment of the main disorder. This circumstance must not, however, lead us to neglect local treatment entirely.

The attempt must be made to check, according to the ordinary rules, partly by local applications, partly by internal remedies, the *hemorrhages* which occur in various parts of the body during the course of the disease. In *epistaxis*, in order to prevent as much as possible the exhaustion of the patient, an early

use of the tampon and the application of cold are advisable; in *hemorrhages from the stomach and bowels*, the swallowing of pieces of ice or alum-whey, and the application of large bags of ice to the abdomen; in hemorrhages from the *urinary passages*, the internal use of tannin which acts locally on these parts: in bleeding from *cutaneous ulcers*, compression or ligature of the eroded vessels, as well as the application of the solution of the chloride of iron to the bleeding surfaces, and, if required, the actual cautery, etc. The acetate of lead and the ergot of rye given internally in large doses, deserve special mention, as remedies which, as a rule, possess great value without reference to the particular site of the hemorrhage.

Of the affections of the *skin* in scurvy the simple interstitial hemorrhages and the petechiæ, ecchymoses and vibices arising from them, and also the slighter forms of dermatitis, require no special treatment. The scorbutic *ulcers* were in former times very often treated locally with the same fresh vegetable remedies which are used with so much success internally in combating the general disease. In many cases it was claimed that local improvement (comp. the observations of Lind and Krebel touching this subject) resulted from the application of slices of lemon, carrot poultices, crushed herbs (cochlearia, sedum acre, etc.), or brewers' yeast to the ulcerated surfaces. In no one case, however, was satisfactory evidence adduced to show that the improved appearance of the ulcerated surface was due exclusively to these local applications, and not at all to the simultaneous internal use of the same remedies. In recent times, apart from the energetic employment of the dietetic and medicinal measures directed against the general disorder, which constitute, at the same time, by far the most effectual treatment for all the localizations of the disease, the cutaneous ulcers receive only the usual surgical treatment of atonic ulcerations. This, as is well known, in addition to cleanliness and careful local disinfection, consists principally in the application of astringent or aromatic water dressings. The hemorrhagic inflammatory *affections of the subcutaneous connective tissue, the periosteum, the bones, cartilage and articulations*, which are met with in severe cases of scurvy must, like the cutaneous ulcers, be treated according

to general surgical rules, since we do not as yet possess and probably never shall discover any effective local treatment specially directed against the scorbutic nature of the troubles. At all events, the lotions and fomentations with water, diluted vinegar, spirits of camphor, and other aromatic and spirituous fluids, which have been recommended with this view, although they may have proved very beneficial in many cases, cannot be counted in the category of the special antiscorbutic local remedies.

In the *hemorrhagic inflammations of the serous membranes*, especially of the *pericardium* and the *pleura*, if the exudation should become so extensive that life is directly endangered through the mechanical interference with the respiration and circulation, the removal by operation of the hemorrhagic fluid would certainly be indicated (of course with strict observance of the usual and necessary precautions). In consequence, however, of the very dangerous character of the operation of paracentesis, when performed on the pericardium, it should only be resorted to in cases of the most urgent necessity. In this respect scorbutic *pericarditis* presents the same indications as inflammation of the serous sac arising from other causes. The case is different in regard to the removal of *pleuritic* exudations. Here, on account of the trifling nature of the procedure, and the freedom from danger of the aspiration method, which has lately come into general use, the operation may very properly be resorted to as freely and as often as in the treatment of ordinary pleuritis. For the rest the same rule, which we have repeatedly mentioned as possessing a general application to the localizations of scurvy, applies with special force to the inflammations of the serous membranes, *i. e.*, without appropriate treatment of the constitutional disorder in which they take their root, they do not show the slightest tendency to recovery, while, on the contrary, under a properly conducted general treatment, they often vanish as it were spontaneously and with astonishing rapidity, simultaneously with the disappearance of the scorbutic cachexia. Hence, in the treatment of these inflammatory processes the greatest weight must, at all events, be laid upon the measures directed against the cachexia, and, if necessary, recourse may be

had, with more or less hope of success, to special treatment, according to the ordinary principles of therapeutics.

The same may be said of the treatment of the *scorbutic affections of the eye*, for a detailed account of which we refer the reader to the text-books and the more extended works on ophthalmology. With regard to the *hemeralopia*, which is quite frequently met with as a complication or sequel of scurvy, we have already mentioned in the section on complications, that it usually disappears simultaneously with the scurvy, when the dietetic treatment indicated for the latter is employed. We also stated that this peculiar behavior proves that there exists a pretty close, although not yet accurately definable, genetic connection between it and the scurvy. In regard to the treatment of other complications of scurvy we must refer in general to the appropriate chapters of this Cyclopædia (see in particular Malarial Diseases, Dysentery, Syphilis). Before concluding, however, we must mention expressly that the existence of scurvy, with its pregnant symptoms of weakness and its hemorrhagic inflammatory diathesis, necessitates the greatest prudence and care in the selection of the methods of treatment, and that this general disorder must often be overcome before the correct treatment of the complications can be entered upon with sufficient confidence.

Morbus maculosus Werlhofii.

Syn.: Purpura hæmorrhagica.

P. G. Werlhofii opera òmnia collegit et auxit J. E. Wichmann (Hanover, 1775). pp. 425, 540 et 748.—*Harless*, Hufeland's Journal. 1800. p. 1.—*J. E. Gauthier Bellafonds*, Essai sur la maladie tachetée hémorrhagique de Werlhof, etc. Paris, 1811.—*Rudolph.* De morbo maculoso hæmorrhagico Werlhofii. Ber. 1811.—*Wentzke*, De morbo maculoso Werlhofii. Diss. inaug. Ber. 1820.—*Hergt*, Ueber Werlhof's Blutfleckenkrankheiten. Leipzig, 1829.—*Rayer*, Hautkrankheiten übersetzt von Stannius. 2. Aufl. (1839). Bd. III. S. 147.—*Schönlein*, Spec. Pathologie und Therapie (herausgegeben von seinen Zuhörern). Bd. II. S. 41 (1841).—*Simeons*, Heidelberger Annalen. Bd. II. 2. S. 979.—*Wunderlich*, Handbuch der Pathologie und Therapie (1856). Bd. IV. S. 584.—*Sander*, Deutsche Klinik (1862). S. 9.—*Chambers*, Lancet T. I. 10. March, 1864.—*Nysseus*, Presse médicale. 1864. No. 4.—*Reder* (Hebra), in R. Virchow's Handbuch der spec. Pathologie und Therapie. Bd. III. 4. S. 719 ff. (1865).—*Lederer*, Wiener med. Presse (1868). Bd. IX. S. 29.—*Henoch*, Berl. klinische Wochenschr. Bd. V. (1868) No. 50.—*Halbermann*, Beitrag zur Erkenntniss der Purpura. Inaug. Diss. Bonn, 1869.—*Dahlerup*, Bibl. for Läger. 5 R. XX. p. 174.—*Mollière*, Recherche clinique sur la nosographie du purpura hæmorrhagica, etc. Lyons, 1874.—*Henoch*, Berl. klin. Wochenschrift. Bd. XI. (1871). Nr. 51.—*Scheby-Buch*, Deutsch. Arch. f. klin. Med. Bd. XIV. S. 466.—*H. Rohlfs*, Memorabilien. Bd. XX. S. 433.

General Nature of the Disease.

The names *Purpura hæmorrhagica* and *Morbus maculosus Werlhofii* have, since the time of Werlhof, been applied to those very peculiar and rare cases of *acquired* and *transitory hemorrhagic diathesis*, which, on account of their *sporadic occurrence* and their relatively *brief duration*, and moreover also on account of the *obscurity of their etiology* and the *apparent spontaneity of their development*, cannot be classed under *Hæmophilia*,

Scurvy, or the ordinary *symptomatic* tendency to bleeding. With regard to the last it must be remembered, that the hemorrhagic diathesis is frequently observed as a consecutive or accompanying symptom of certain severe acute or chronic diseases, such as variola, typhus exanthematicus, phosphorus-poisoning, leukæmia, progressive pernicious anæmia, protracted icterus, etc. In such cases, however, since it has developed on the foundation furnished by another well-defined primary disease, it must be regarded and classed as purely *symptomatic*, so far as its clinical nature is concerned. Strictly speaking, the same is true also of the hemorrhagic diathesis of scurvy, for in that disease the tendency to hemorrhage is usually not observed until after the scorbutic general disturbance has set in, and, furthermore, the hemorrhages when they occur have in all probability a direct causal connection with the pre-existing cachexia. The cases designated as "Morbus maculosus" differ from those of scurvy and from those of the ordinary symptomatic hemorrhagic diathesis in this, that the affection possesses more or less distinctly the character of an *essential disease*, that is to say, the tendency to hemorrhage, although sometimes very marked, cannot be sufficiently explained either by the anamnestic data or by the somatic conditions of the patients, and cannot be made more intelligible by analogy with other similar observations. As *prototypes* of the disease in question, we can therefore take only those cases in which the hemorrhagic diathesis is developed *suddenly* and *unexpectedly* at any period of life in *individuals previously healthy*, and in which it cannot be considered, as can many anomalous cases of hæmophilia, as *the result of an inherited predisposition*. Less typical, and therefore in their clinical bearings the subject of much controversy, are: first, certain cases which differ in many cardinal points from the clinical picture of scurvy, but, nevertheless, on account of the *external conditions* under which they develop, present a certain, although usually only an apparent etiological similarity with the latter disease; secondly, cases which occur in individuals still suffering or recently recovered from some other disease, and which, although the connection is merely external and accidental, remind us of the *symptomatic* hemorrhagic diathesis from the

fact that the affected persons were not previously in perfect *health;* thirdly and lastly, those cases in which the hemorrhagic phenomena are decidedly the most prominent symptoms, but in which *other pathological phenomena* are also observed which cannot be regarded as *directly* and *immediately dependent* upon the hemorrhagic diathesis, or upon the hemorrhages that have taken place. We will presently discuss in detail the nature of the most frequent of the concomitant phenomena alluded to in this third category, and also the appropriateness, to these complicated cases, of the name given to the disease. It is necessary first to consider briefly the hemorrhagic diathesis, since it presents itself in the individual cases of morbus maculosus under different forms and in varying degrees of intensity. These variations are not, it is true, of essential importance, but they have led pathologists to constitute subdivisions of the disease with different names.

Hebra, Reder, and other authors, denominate as "*Purpura simplex*" that simplest form of the disease which consists *exclusively* in the development of minute petechiæ, while throughout the whole course of the affection no extensive interstitial cutaneous extravasations and no hemorrhages into other parts take place. If, on the contrary, in addition to these minute petechiæ, larger spots and even extensive ecchymoses and vibices appear upon the general surface, and if further, in addition to the skin, internal parts, such as the mucous and serous membranes, are attacked by the hemorrhagic diathesis, the same authors denominate the disease as "*Purpura hæmorrhagica.*" In many text-books the milder form of morbus maculosus, the purpura simplex, on account of the insignificance of its clinical and anatomical characters, is classed, not among the general hemorrhagic diseases, but among the local affections of the skin. Experience teaches, however, that morbus maculosus very frequently begins as a so-called purpura simplex, which later develops into a purpura hæmorrhagica, in consequence of the supervention of extensive cutaneous extravasations and internal hemorrhages. Hence, since it is impossible in any given case of purpura simplex to predict with certainty that it will run its whole course strictly as such, the systematic subdivision of the

disease into these two varieties must be regarded as purely conventional and artificial. We therefore prefer to treat of purpura simplex also among the general disturbances of nutrition. Like purpura hæmorrhagica, it is in our opinion one of the forms in which Werlhof's disease shows itself. It may be defined as a mild and very rudimentary form of this pathological species, which may either remain in this embryonic stage until recovery sets in, or may at any moment be transformed into the severer form of the disease.

In point of severity and development, purpura simplex and purpura hæmorrhagica, therefore, are simply different grades of the same essential hemorrhagic disease. It must be well understood, however, that for the development of this disease, it is essential that there should be no other primary disturbances in the given cases. That, on the other hand, the secondary symptoms, especially such as characterize general anæmia, will not be wanting after the occurrence of profuse hemorrhages, is too self-evident a fact to require explanation, or consideration here. We must, however, investigate at this point the question whether we should or should not include under the head of morbus maculosus, those cases of spontaneous hemorrhagic diathesis which present a somewhat more complicated clinical history. In this connection we must mention first, that, while many cases both of purpura simplex and purpura hæmorrhagica run their course *unaccompanied by fever* (*purpura non febrilis*), others, on the contrary, exhibit febrile movements (*purpura febrilis*) without there being any special reason, any apparent anatomical cause, for the elevation of temperature. The fever in these cases may occur only at the height of the disease, or at least not for a considerable time after the first extravasation of blood takes place, or it may actually precede and usher in the hemorrhagic symptoms. The cases belonging to the first variety can unconditionally and unhesitatingly, for reasons yet to be given, be classed as morbus maculosus, but there is some reason to doubt the clinical connection of the cases which present a febrile prodromal stage, with ordinary purpura, and we do not believe that satisfactory proof of the identity of the two can be adduced. Notwithstanding this fact, however, we are compelled to con-

sider here also this second form of purpura febrilis, because it is scarcely possible to place it in any other part of the pathological system, and because, moreover, not a few of these cases correspond, in every respect, with the exception of the fever, with those of purpura non febrilis. A somewhat greater variation from the typical form of the latter affection is presented by certain cases in which either with or without a prodromal fever other more local disturbances precede for a short time the hemorrhages, and frequently also persist as long as the latter. These local disturbances are often of a *rheumatic* character; they consist especially in pains or painful swellings of one or several joints. The question at once suggests itself, whether these cases of so-called *purpura rheumatica* are also to be classed as morbus maculosus or not? On the authority of Schoenlein, who introduced it into pathology as a separate and special disease, the much spoken of *peliosis rheumatica* was for a long time believed to be a peculiar rheumatic-hemorrhagic affection entirely distinct from the morbus maculosus Werlhofii. Under that name Schoenlein, as well as Fuchs, Canstatt, and others, understood a hemorrhagic disease, characterized by extravasations into the cutaneous layers alone without any internal hemorrhages; these extravasations are in the form of small petechiæ, but the affection is distinguished from purpura simplex by the fact that the bleeding is preceded by pain in the joints and frequently by fever. Although, as before remarked, the clinical picture thus produced has been generally regarded as a distinct and typical disease, or a pathological species sui generis, Scheby-Buch[1] has lately proved, by direct observations, the existence of transition cases between the so-called peliosis rheumatica and purpura hæmorrhagica. He observed namely cases which began like peliosis, with fever, pain in the joints, and consecutive petechial exanthem, but subsequently exhibited, as in purpura hæmorrhagica, extensive extravasations into the skin and internal hemorrhages. It need scarcely be remarked that the occurrence of these cases makes the existence of peliosis rheumatica, as an independent disease, very questionable. It appears to us,

[1] Deutsches Archiv für klinische Medicin. Bd. XIV. S. 466.

therefore, advisable to discard peliosis rheumatica as a distinct disease from our nosology, and to employ for all the forms of essential hemorrhagic diatheses which commence or are accompanied by rheumatic symptoms, the more general and less objectionable name of purpura rheumatica. We must, however, —and here we are in perfect accord with Scheby-Buch[1] and Senator,[2]—insist explicitly on the non-identity of these cases with those rather infrequent cases of acute articular rheumatism, in which, in consequence of the development of an endocarditis ulcerosa, and the resulting embolism, multiple extravasations are produced. It is, at all events, very noteworthy that purpura rheumatica never develops into severe articular rheumatism; that, further, the profuse sweats so constantly present in the latter are entirely wanting in the former disease; and finally, that it has no tendency to be complicated with endocarditis. It is evident from these facts that purpura rheumatica is not a special form of acute rheumatism, and hence it cannot correctly be designated by such names as Rheumatismus petechialis, Rheumatismus hæmorrhagicus, etc. On the contrary, it is probably more correct to assume, with Scheby-Buch, that the rheumatoid articular affections in the cases in question are dependent upon the hemorrhagic diathesis, with which they possess some close causal relation. Upon this assumption, which cannot, however, as yet be positively proved, we regard purpura rheumatica as a sub-variety of morbus maculosus. In what follows we will, therefore, study it in connection with the ordinary, non-rheumatic form of the disease.

Finally we will have to call attention, when considering the symptoms of morbus maculosus, to the occurrence, in certain cases, of severe gastric disturbances which complicate still further the clinical history of the disease (Henoch, Scheby-Buch). In our opinion, however, it is not difficult to furnish good evidence to prove that such cases do not form an independent pathological class, but that they belong properly in the general family of the essential hemorrhagic diathesis (morbus maculosus).

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[1] l. c. S. 528.

[2] Vol. XVI. of this Cyclopædia.

Etiology.

Cases of hemorrhagic diathesis which, in accordance with their clinical history, must be classed as morbus maculosus Werlhofii, occur at all periods of life, in both sexes and in every possible form of physiological constitution. Still, it would appear from the literature of the subject (H. Marsh, Churchill, Stokes, Hunt, Law, Rilliet and Barthez, and others), that the predisposition to the affection is relatively greatest during the period of adolescence, namely, from the fifteenth to the twentieth year of life. According to Curran, the female sex is in general somewhat more disposed to it than the male. Strong and plethoric individuals cannot by any means be said to possess an immunity from the disease, since in quite a number of the cases that have been observed, the patients were previously perfectly healthy and robust in every respect. Still, the majority of the cases have occurred in subjects of a weak and anæmic constitution; it must be distinctly stated, however, that, at the time of the outbreak of the hemorrhagic diathesis, none of the cases reported by us and others were suffering from the extreme forms of progressive pernicious anæmia. (With reference to this subject see Vol. XVI.) No inherited predisposition to the diathesis can be demonstrated in any way; on the contrary, the sporadic character in respect of both time and place, as well as the transitory nature of the disturbances, is highly characteristic of morbus maculosus. Observations have been recorded, however, which prove that the disease can occur in the same individuals at longer or shorter intervals, and hence demonstrate the existence in certain persons of an evident individual predisposition to the disease. We are still entirely ignorant of the nature of this predisposition, but it probably depends upon congenital peculiarities. It would not be justifiable to classify such cases at once as hæmophilia, since not only the facts that the affection has not been inherited from the parents, and can not be transmitted to the offspring, but also the fact that during the intervals the patients enjoy entire immunity from the hemorrhagic tendencies, prove that we have to deal with a very different affection.

Finally, in connection with the individual predisposition to morbus maculosus we must also mention here the occurrence of the affection in convalescents from all sorts of severe diseases, for instance, typhoid fever, and other exhausting processes. Here the persons affected can by no means be said to be healthy, in the ordinary sense of the word, but still less can they be said to be actually sick, and hence the developing hemorrhagic diathesis cannot be properly regarded as symptomatic. Personally we have been led by a number of observations made by ourselves, to believe that the predisposition of convalescents to morbus maculosus is greatest exactly at that period of the progressing recovery when the pallor and weakness are fast disappearing, when they make their first attempts to walk, and when the returning appetite demands an increased supply of food; at a time, consequently, when they cannot longer be said to be "sick" in the usually accepted sense of the word. We intend, when considering the essential character and the pathogenesis of the disease, to return again to these cases of morbus maculosus, and we will then state more definitely our views respecting their possible mode of occurrence.

Very little is known concerning the determining causes of morbus maculosus. In very many of the cases the disease is developed, to all appearances, spontaneously, and affects persons whose bodily health and hygienic surroundings have previously been excellent. In other cases, it is true, the patients had previously been in needy circumstances, lived in unhealthy houses or on insufficient food, etc., but still, it would be improper to lay too much stress, in the etiology of the disease, upon these points, since countless individuals are constantly subjected to such influences, while the disease in question is essentially rare. In other words, we cannot subscribe to the hypothesis which makes morbus maculosus actually nothing more than a mild form of scurvy. The non-identity of the two processes is demonstrated not only by important differences in the manner in which they begin, and the course which they run, and by not less striking differences in the symptomatology, but more clearly still by the simple fact, that a *cumulative outbreak of that form of the hemorrhagic diathesis*, which, *by rea-*

son of its clinical characters, must be designated not as scurvy, but as *morbus maculosus*, has never yet been observed in communities where all are living under the same hygienic surroundings. On the contrary, morbus maculosus always occurs *sporadically*, while scurvy generally prevails as an epidemic. A peculiar nomenclature, which is entirely incorrect and indefensible, has been based on the supposed identity of the two morbid processes; according to it, morbus maculosus figures in many text-books as "Land-scurvy," just as if the severe form of scurvy, in its more restricted sense, could occur only at sea, and has not appeared sufficiently often on land.

It is evident, from the foregoing, that the etiology of morbus maculosus, both as regards the nature of the individual predisposition, and the determining causes, is still involved in almost complete obscurity. We may even assert, and this is a point which may prove of diagnostic importance, that *the less we can discover and positively affirm concerning the etiology* of a case of transitory hemorrhagic diathesis, the greater is the probability that it belongs in the category of morbus maculosus.

Pathology.

General Features of the Disease.

Morbus maculosus often begins acutely and at the same time in a very characteristic manner. In such cases there are no prodromal warnings, such as local disturbances or a general state of ill-health, the first indication of the existence of the hemorrhagic diathesis being the appearance of petechiæ upon the skin or the occurrence of some other hemorrhagic symptom, *ex. gr.*, epistaxis. Besides these specially pure and typical forms of the disease, there occur others in which the hemorrhagic symptoms are preceded for several days by mild prodromal symptoms of an undecided character, such as slight languor, headache, loss of appetite, and sometimes even moderate fever. These prodromi usually last only one or two days, rarely longer than a week. A *marked initial cachexia*, like that which so generally precedes

scurvy, *is never observed.* Finally, some cases begin with *rheumatic* symptoms, and to such the names Purpura rheumatica or Peliosis rheumatica have been applied. Painful sensations are experienced in certain joints, particularly in those of the lower extremities (the knees and ankles). These pains may, or may not, be accompanied by slight fever. They continue several days, and are sometimes attended by slight swelling of the joints. The exanthem then appears, and simultaneously with its development the articular affection, as a rule, abates.

The *development and extension of the cutaneous hemorrhages* are always painless, and are not preceded by any hyperæmic redness of the skin. The extravasations often cover *the entire body.* It has been said that the skin of the face is not at all, or at least very rarely, affected in morbus maculosus. We cannot agree with this statement, since in several cases we have seen not only petechiæ, but even extensive ecchymoses, which were unquestionably not of traumatic origin, upon the face, and especially on the upper eyelids and the margins of the orbits. The hemorrhagic exanthem, however, is usually most abundant on the lower extremities, and next to them on the trunk. On the latter, in the severer forms of the affection, the number of purpura spots may amount to many hundreds. In some, but not in all of the cases designated as peliosis rheumatica, it has been observed that the petechiæ appeared first in the neighborhood of the painful joints, and spread gradually from them to more distant parts of the body.

The individual spots vary greatly in size, ranging generally from that of a large pin-head to that of a lentil, a pea, or a bean. The larger ecchymoses and vibices (compare the preceding chapters on Hæmophilia and Scurvy) are much less frequent than the smaller spots, but they occur here and there upon the surface in nearly every decided case of purpura hemorrhagica. In shape the smaller spots are often, and perhaps generally, round, but star-shaped and irregular spots are not at all rare among them. The larger ecchymoses assume every possible form. The hemorrhages are not so exclusively confined to the regions of the capillary network of the hair follicles as is the case in the other petechial exanthemata. We find, it is true,

numerous petechiæ which are pierced through the centre by a hair, but we usually find many spots, both small and large, which do not present this peculiarity. Finally, in morbus maculosus, as well as in scurvy, we find, in addition to the *maculæ, more or less numerous vesicles*, which are evidently produced by circumscribed hemorrhages into the rete Malpighi from the capillary loops of the papillæ of the skin.

The *color* of the fresh spots is the same as in other hemorrhagic efflorescences—namely, a dark bluish-red. It does not alter on pressure, but as time passes on it changes successively to greenish-blue, brown, and yellow (compare the descriptions of Scurvy and Hæmophilia). It is exceedingly common for *fresh crops* of the petechial eruption to appear at varying intervals during the course of the disease. When several such relapses have occurred, the body of the patient presents a very odd appearance, since the spots, which vary greatly not only in size and shape, but also, owing to their different ages, in color, are scattered about in a most irregular manner. With regard to these relapses we must also mention that, like the first outbreak of the exanthema, they are frequently ushered in by slight fever and pains in the joints. Sometimes the process described above is repeated several times, with great exactitude, each fresh outbreak of the eruption being attended by a modification of the premonitory symptoms. In other cases, on the contrary, there is no concurrence in point of time between the intercurrent development of fresh elevations of temperature and articular pains on the one hand, and of fresh cutaneous hemorrhages on the other, the relations of these different symptoms to one another being very irregular.

The occurrence of the majority of these relapses of the hemorrhagic exanthema does not, by any means, seem to be dependent upon special external causes; like the hemorrhagic diathesis in general, they are apparently perfectly spontaneous. Still, in many cases they are dependent upon some mechanical injury, or upon some change in the functional activity of the heart, etc. Just as in scurvy, we find that suggilations appear at points where the skin has been subjected perhaps accidentally to unusual pressure or to some other slight injury, or a

relapse of the purpura eruption occurs, and a fresh crop of spots appears particularly on the lower extremities, when the patient makes some active movement—for instance, when after having been confined to bed for some time, he makes his first attempt to get up and walk about.

In many, but by no means in the majority of the cases, the hemorrhagic diathesis manifests itself clinically only by the eruptions on the external surface (purpura simplex). It is far more frequently attended also by *hemorrhages in other parts* (purpura hæmorrhagica proprie sic dicta). These may happen at any time during the course of the disease, even at its very beginning. There is also a class of intermediate cases in which the visible mucous membranes, viz., those of the mouth, pharynx, and eyes, exhibit more or less extensive interstitial extravasations, without any free hemorrhage from their surface.

Generally, however, the symptoms of the hemorrhagic diathesis are not so limited, the interstitial extravasations being accompanied, as a rule, by more or less *copious*, *superficial hemorrhages.* Profuse and exhausting hemorrhages from the superficial and deep mucous membranes, namely, from the nose, stomach, intestines, urinary passages, genitals in women, and bronchi, are much *more common* in morbus maculosus than *even in severe cases of scurvy.* Hemorrhages from the mucous lining of the mouth, and particularly the gums, also occur, but the bluish-red discoloration, the softening, swelling and spongy character of the gums, as well as the excessive sensitiveness of these parts which is very generally present in even the mildest cases of scurvy, are entirely wanting. If we examine the gums after removing the coagulated blood, which frequently covers them, we will find them,even in cases where no teeth have been lost, either perfectly normal in color and consistency, or oftener still somewhat pale and bloodless, but never bluish-red or swelled. In morbus maculosus consequently all the signs of a hemorrhagic *inflammation* of the gums *are wanting.* This fact will be found to possess considerable diagnostic importance.

In Werlhof's disease *hemorrhages also occasionally occur within the serous cavities*, viz., the pleura, the pericardium, and the peritoneum, and also in the *meninges and in the substance*

of the brain.[1] They take the usual course of such accidents, generally ending fatally. These complications are, however, decidedly exceptional, as is also the formation of extensive hæmatomata in the subcutaneous connective tissue. A participation of the muscles in the hemorrhagic accidents has occasionally been observed, but it is by no means common.

The hemorrhagic symptoms on the part of the skin and mucous membranes constitute consequently the most important and essential part of the clinical picture of morbus maculosus. We may in this place expressly state it as a fact that in many cases of the disease there are absolutely no other symptoms, either local or general, of illness. When, for instance, the disease affects persons previously strong and healthy, and is not accompanied by fever or rheumatic affections of the joints, and when, further, the surface hemorrhages from the mucous membranes are not too frequent or abundant, the general health of the patients may be almost unaffected throughout the entire course of the disease. This state of subjective good health then presents a striking contrast to the objective appearances. When, on the contrary, the hemorrhages are often repeated and copious, and especially if the patients were previously anæmic, we cannot wonder at the consecutive appearance of symptoms showing an alarming degree of anæmia: for instance, pallor, dropsical swellings, extreme weakness, fainting fits, etc. Nor is it surprising that in many of these cases death should occur under the symptoms of acute oligæmia. Still, although the condition of the patients is often alarming, a fatal termination is in general not very frequent. The sickness ends by far more frequently in recovery after the expiration of one or two weeks. In other cases the disease is more protracted because of the repeated recurrence of the hemorrhages now in one form, now in another; it is only when they have finally ceased that improvement sets in, and the pale and exhausted patients gradually regain strength and health.

Certain authors, particularly Henoch,[2] have reported cases

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[1] *Tardieu*, L'Union. 1870. No. 48.

[2] Berl. klin. Wochenschr. 1858. Nr. 50; ferner, 1874. Nr. 51.

which differed somewhat in their course from those above described. These cases presented a peculiar, more or less idiopathic diathesis of a transitory character, but in addition to the fever and purpura, and also to marked articular affections, which, however, were not present in all of them, they exhibited *severe gastric and intestinal symptoms.* These consisted chiefly in vomiting of bilious matters, meteorismus and tenderness of the abdomen, and severe colicky pains; they recurred several times during the course of the disease. Although the recurrence of these symptoms is not mentioned in other treatises on the disease, we cannot understand why Henoch should be inclined to regard such cases as constituting a special form of disease, entirely distinct from morbus maculosus. We believe, with Scheby-Buch,[1] that the explanation of such cases lies in the assumption that the digestive apparatus is involved in the hemorrhagic process, that we have to deal probably with hemorrhages in the serous coat of the stomach and intestines.

Post-Mortem Appearances.

When death occurs in the course of morbus maculosus it is almost invariably, as far as we yet know, the result of too frequent and copious hemorrhages. The dead body is exceedingly pale in consequence of the loss of blood; it is frequently somewhat œdematous, and is usually covered with numerous petechial spots, both old and recent, large and small. The condition of the general nutrition depends upon the duration of the disease; in the cases which prove rapidly fatal it is in general unaltered, but in those which have run a protracted course it is somewhat impaired. All the internal parts, like the skin, present an anæmic appearance, on account of the diminution in the quantity of blood contained in them. The mucous membrane of the lips, tongue, gums, hard and soft palate and pharynx is usually covered with blackish, half-dried blood crusts. Upon removing these the membrane sometimes appears pale but otherwise normal, sometimes presents superficial erosions, and, finally, is some-

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[1] l. c. S. 490.

times more or less thickly covered with small ecchymoses. Similar erosions and ecchymoses are also met with, often in immense numbers and spread over a very large space, on the mucous membranes of the stomach, intestines, the pelvis of the kidneys, the ureters, the bladder, the female genitals, etc. They are less frequent upon the mucous surfaces of the air-passages. The contents of the stomach and intestines are often mixed with large quantities of loosely coagulated or still fluid blood. The bronchi contain bloody mucus and sometimes freshly exuded blood in considerable quantities. Occasionally, but not often, blood is found in the pericardial, pleural, and peritoneal cavities. Multiple interstitial extravasations in the tissue of the serosæ, and small collections of blood in the subserous connective tissue, are much more common. In other respects the tissues of the pericardium, pleura, and peritoneum in such cases are approximately normal or merely somewhat hyperæmic. The extensive, fibrinous exudations on the surface and the other macroscopic inflammatory changes, which are so common in the fatal cases of scurvy in which these membranes have been involved, are wanting in morbus maculosus.

Very little is known of any other constant anatomical changes. We have no exact data respecting the appearances of the articular cavities and ligaments in the cases which were complicated during life by rheumatic symptoms. On this subject there exists only a single publication which emanates from Traube's clinic. The case was one of "peliosis rheumatica," in which, *post-mortem*, the synovial membranes of the affected joints were found somewhat injected, and the quantity of the slightly clouded synovial fluid somewhat increased (Leutholdt[1]). Of the condition of the walls of the vessels, particularly of the capillaries, we are also almost entirely ignorant.[2] It is very probable, however, that in these cases, just as in other fatal cases of anæmia due to excessive loss of blood, a fatty degeneration of the vascular tissues and of the muscles of the heart has taken place.

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[1] Berl. klin. Wochenschrift. 1865. No. 40.

[2] In one case *Wilson* discovered amyloid degeneration of some of the capillaries in the immediate neighborhood of a few of the petechiæ. Brit. and Foreign Med. and Chirurg. Review. 1856. Oct. p. 480.

In a majority of the autopsies the heart has been found relaxed and its muscular substance pale. The valves, as far as is known, were perfectly normal, apart from some unimportant changes, and the cavities of the organ, in correspondence with the general anæmic condition, contained very small quantities of loosely coagulated blood.

Very few reports of the condition of the blood during life have been published, and even they are in many points at variance with one another. Its color is said to be usually rather dark in recent cases; in older cases, on the contrary, especially when copious hemorrhages have occurred, it is bright. A genuine oligocythæmia, therefore, does not appear to exist primarily in morbus maculosus; when it occurs it is developed at a later period, and is due to the hemorrhages (for an example of the reverse see Progressive Pernicious Anæmia). In a case recently observed by us in the clinic at Basel, which was very severe, but nevertheless terminated in complete recovery, the relative proportions of the red and white blood-corpuscles to one another was perfectly normal during the first days of the disease, but subsequently the white corpuscles slightly exceeded the red in number. This condition, however, could be regarded only as an instance of that form of moderate leucocytosis which is known to be a regular result of copious hemorrhages. In the case referred to, the color of the blood corresponded with its microscopic appearances; it was at first perfectly normal, but afterwards became somewhat paler. Its coagulability was not affected. Albers' experience in this last respect agrees with ours: he states that the blood of persons suffering from purpura hæmorrhagica does not lose its capacity for coagulation. Other observers, however, particularly Legrand, Rayer, Biett, and Becquerel, state that they have found the blood very little or even not at all coagulable. Of the quantitative relations of the solid constituents of the plasma to one another, nothing is at present definitely known, nor do we know whether or not any abnormal substances are present in the blood.

The spleen and lymph glands present no constant changes. The first-named organ, however, has repeatedly been found enlarged, and its pulp was then of a pasty consistency (Bill-

roth,[1] and others). In a case examined by Ponfick,[2] the medulla of the bones in various parts of the skeleton was found to contain numerous large and small hemorrhages.

Special Symptomatology.

Analysis of the Pathological Symptoms and of the Anatomical Appearances.

The pathological symptoms of morbus maculosus which we have described above, may be divided according to their nature into *four* classes. It must be admitted, however, that they are not present with equal completeness, or in the same grouping and combination in all cases. The first, and under all circumstances the most important of these classes, is constituted by the *hemorrhagic* symptoms, which are characteristic of the affection, and without which the existence of the disease is unimaginable. The *second* class includes the *febrile* symptoms, which either precede the hemorrhages or are developed intercurrently. They are, however, not unfrequently entirely wanting. Still less uniformly present, either as precursors or attendants of the hemorrhages, are the symptoms included in the *third* class, viz., the rheumatic pains and swellings of the joints, which are observed in the cases described as purpura (peliosis) rheumatica. We have seen that these symptoms sometimes do and sometimes do not possess a definite connection with the fever, and also that they may accompany the hemorrhagic accidents even when fever is entirely wanting. Finally, the *fourth* class comprises those severe gastric and intestinal symptoms which are met with in a few cases, and of which we spoke at the close of the section on general symptomatology.

The *cutaneous hemorrhages* as well as those of *internal parts* in morbus maculosus are in general *simple extravasations*, that is, they are not dependent on any *intense local hyperæmia or inflammation.* That the cutaneous and other hemorrhages are not due to inflammation is evident both from the fact that

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[1] Virchow's Archiv. Bd. XXIII. S. 465. [2] Ibidem. Bd. LVI. 4. S. 534 (1872).

the cutaneous petechiæ and ecchymoses are not preceded by any roseolar or erythematous rash, and from the anatomical lesions in the internal viscera which were the seat of hemorrhages intra vitam. In morbus maculosus, therefore, one may properly speak of the existence of *a hemorrhagic, but not, as in scurvy, of a concomitant inflammatory diathesis.* In the development of the overwhelming majority of the individual hemorrhagic foci and free hemorrhages which occur in morbus maculosus, neither external mechanical injuries nor increased force of the heart's action can be said to have a causative influence. On the contrary, their origin is apparently spontaneous. Hence, it is necessary to seek for the immediate cause of these foci and free hemorrhages, in some diseased condition of the walls of the capillaries, in consequence of which they are more easily ruptured, or at least become more permeable to their fluid and solid contents. These supposed structural changes in the capillary walls, however, must be of the most delicate and imperceptible kind, since pathological anatomists are as yet entirely unable to give us a description of them. Some further remarks upon this subject will be found in the section on the "Nature and Pathogenesis of the Disease."

The analysis of the *febrile* symptoms in morbus maculosus furnishes support for the opinion that the fever, when present, is not always due to the same cause, and has not always the same clinical significance. The genesis of the fever is naturally most inexplicable in those cases in which the abnormal elevation of temperature precedes the hemorrhages, and is not accompanied by any other abnormal phenomena, such as the articular symptoms. Here there are no anatomical changes which could account for the occurrence of the fever, and hence we must, for the present, relinquish all hope of explaining it. The case is not much better with regard to that fever, which in connection with articular pains not unfrequently ushers in the cases of so-called purpura (or peliosis) rheumatica, since, to us at least, it does not seem by any means certain or even probable that this fever is directly dependent upon and symptomatic of the affection of the joints. These cases may be contrasted, on the one hand, with others in which the same articular pains and swellings

without fever initiate the disease, and on the other hand, clinical experience has taught us that an initial fever may exist *without* articular symptoms. It is easier to explain the occurrence of fever *during the course of the disease*, at a time consequently when numerous hemorrhages have already taken place, and collections of extravasated blood have formed at various places throughout the body. In these cases, just as in analogous cases in other diseases, there is reason to suppose that many of the febrile movements are of a *resorptive* nature, being symptomatic of the process of involution which is taking place in the collections of effused blood; furthermore, that the blood, which has been extravasated into the interstices of the tissues, may sometimes act as an *inflammatory irritant* on the surrounding parts, and thus cause slight fever. Finally, however, there is another possible and very different mode, in which the fever may arise in some cases, namely, the one which we have chosen as the most probable one for the fever of progressive pernicious anæmia (comp. Vol. XVI.). It will be remembered that, in the place referred to, we expressed our belief in the opinion that there exists a special "anæmic fever," or that a predisposition to febrile movements accompanies the more intense grades of anæmia, and is the immediate result of the excessive poverty of the blood.

To save repetition, we will refer the reader to that article for the proofs that have been adduced in support of this hypothesis. Here we must point out, however, that the excessive losses of blood in severe cases of morbus maculosus may produce in a short time as extreme degrees of anæmia as are met with in the latter stages of progressive pernicious anæmia; and that consequently a fever which appears during the course of the former disease, at a time when the poverty of the blood is greatest, and which decreases and disappears coincidently with the anæmia, may with perfect propriety be called an "anæmic fever" in the sense in which we have used that phrase. That there are cases of febrile morbus maculosus in which the elevations of temperature actually present a remarkable parallelism with the grade of the existing anæmia, is clearly demonstrated by the case already referred to, which we ourselves observed in the clinic at Basel.

The following notes of the history of this case are taken from the clinical journal.

A. S., sixteen and a half years old, photographer, born in Schleswig-Holstein. His father died recently of phthisis pulmonum et laryngis, and he has lived since with his mother and five brothers and sisters in needy circumstances; states, however, that he was perfectly well until the day before his admission. An inherited or individual predisposition to hemorrhage does not exist. None of the other members of the family have at any time been subject to bleeding, and he states that they are all perfectly healthy. He himself never before suffered from hemorrhagic accidents, and his present sickness came on *suddenly* and without warning.

On the 12th of March, without any apparent cause, and when he was feeling in every respect entirely well, a hemorrhage from his tongue took place. On the following morning the patient noticed several bluish-red spots on his lips, and by noon his entire body was covered with numerous blood-spots of various sizes. Meanwhile his appetite was entirely unaffected, and he had no headache, no pains in the limbs or joints, and in short no subjective disturbances whatever. He was received into the medical clinic on March 14, 1876.

Status præsens: Moderately strong individual, of rather pale complexion. Petechiæ scattered over the face; on the upper and inner margin of the orbit on the left side, a large violet-blue ecchymosis. Exceedingly abundant petechial exanthem on the body and also on all the extremities. The lips and gums covered with blood-crusts. Upon removing them the gums appeared superficially excoriated in many places, but otherwise normal, except that they were somewhat pale. On the lips a few bluish-red spots about as large as a lentil, and on the dorsum of the tongue three bullæ about 0.5 centimetre in diameter, filled with blood. The nostrils on both sides obstructed with dried blood. No abnormities of the heart, lungs, liver, or spleen. Pulse moderately strong and regular, 74. Eighteen respirations per minute.

March 14. Temperature: Morning, 98.6° F. Evening, 98.2° F.

Further course:

March 15. Temperature: Morning, 98.6° F. Evening, 100.4° F.

During the day new petechiæ, *epistaxis.* The ophthalmoscopic examination of both eyes revealed no hemorrhages in the retina. The microscopic examination of the normally colored blood showed no increase in the relative number of the white blood-corpuscles.

March 16. Temperature: Morning, 98.2° F. Evening, 100° F.

Small ecchymoses in the conjunctiva. Upon the body, besides new petechiæ, several large, irregularly shaped ecchymoses. *Gums not spongy, pale. Very dark, bloody urine* was passed several times during the day. General health *wholly unaffected.* Appetite good. Countenance rather pale.

March 17. Temperature: Morning, 98.7° F. Evening, 98.° F.

Urine continues bloody. Two bloody stools. The older petechiæ already greenish

and brownish in color. New petechiæ. Towards evening, *epistaxis*, which was repeated in the night.

March 18. Temperature: Morning, 98.7° F. Evening, 102° F.

Recurring epistaxis so severe as to render plugging of the anterior and posterior nares on both sides necessary. *Persistent hæmaturia and several bloody stools* during the day. The patient feels languid, and is *very pale.* Pulse small, somewhat tense, 84. Respiration regular, and not accelerated. Spleen not enlarged.

From this time, the temperature in the axilla was taken every two hours.

Evening, 7 o'clock, 102° F.; 9 o'clock, 100.5° F.; 11 o'clock, 100.4° F.

March 19.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.	
	T. 100.4°	100.4°	100.5°	99.°	100.4°	100.7°	
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	8 P.M.	9 P.M.	11 P.M.
	T. 101.6°	101.1°	102.6°	102.2°	Sodæ sal.[1] gr. 56	99.5°	98.7°

During the day the blood trickled from the nostrils through the tampon. Bloody urine and stool. Great weakness and pallor.

March 20.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.	
	T. 97.7°	99.5°	99.7°	102.2°	102.6°	101.8°	
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	8 P.M.	9 P.M.	11 P.M.
	T. 101.1°	103.1°	103.1°	103.3°	Sod. sal. gr. 84.	101.1°	96.8°

Delirium. Spleen not enlarged. *Urine no longer bloody. No* stool. Extreme pallor.

March 21.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.	
	T. 100.4°	97.3°	96.6°	98.2°	98.2°	99.5°	
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	8 P.M.	9 P.M.	11 P.M.
	T. 100.4°	100.7°	103.5°	102.6°	Sod. sal. gr. 84	101.3°	99.5°

Tampon removed. No new cutaneous hemorrhages. Urine *free from blood. No* stool.

March 22.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.	
	T. 99.5°	100.°	99.5°	100.4°	101.3°	100.9°	
	1 P.M.	3 P.M.	5 P.M.	6 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 100.9°	102.7°	103.1°	Bath.	99.5°	102.2°	101.3°

Urine and *stool free from blood.* Delirium. Prostration.

March 23.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	10 A.M.	11 A.M.
	T. 102.2°	101.5°	101.3°	103.1°	103.1°	Sod. sal. gr. 84	101.6°
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.	
	T. 101.3° Bath.	99.5°	100.9	102.6° Bath.	103.6° Bath.	101·8°	

No new hemorrhages. Condition unchanged.

March 24.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.	
	T. 101.3°	97.7°	100°	100.4°	100.4°	101.6°	
	1 P.M.		3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 102.2°	Sod. sal. gr. 84.	100.7°	100.4°	100.4°	99.5°	100.4°

Sensorium not yet quite free. Great pallor.

[1] Salicylate of soda.

March 25.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.
	T. 99.9°	97.7°	99.3°	100.°	100.7°	100.7°
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 101.6° Sod. sal. gr. 84.	101.3°	100.4°	98.7°	96.8°	99.2
March 26.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.
	T. 99.5°	99.2°	100.4°	100.4°	100.7°	100.7°
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 101.5° Sod. sal. gr. 84.	100.4°	99.5°	98.7°	98.7°	98.7°

Petechiæ faded. No hemorrhages. Spleen not enlarged.

March 27.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.
	T. 99.°	98.4°	99.2°	100°	101.1°	101.5°
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 102.6°	102.9°	103.1°	101.6°	101.6°	100.7°
March 28.	1 A.M.	3 A.M.	5 A.M.	7 A.M.	9 A.M.	11 A.M.
	T. 99.5°	99.5°	99.°	99.°	99.3°	99.3°
	1 P.M.	3 P.M.	5 P.M.	7 P.M.	9 P.M.	11 P.M.
	T. 99.9°	100°	100.7°	100.7°	100.4°	98.7°

From this on time there was no *fever*. The appearance of the patient improved. Sensorium became absolutely clear. So long as the hemorrhages persisted, the treatment consisted in the subcutaneous injection of ergotin, and the internal use of acetate of lead and ice. Appropriate dietetic rules were enjoined, viz., rest, the horizontal position, and for nourishment nothing but cold milk. The use of the preparations of iron was begun on the 29th of May. Rapid improvement in strength and appearance. He was discharged cured on the 4th of April.

The *rheumatic symptoms in the joints*, which distinguish the cases of so-called *Purpura rheumatica* from other cases of morbus maculosus, form, in respect both to their genesis and to their anatomical nature, an exceedingly obscure chapter in the symptomatology of the disease. In no cases are there any gross nutritive changes in the joints which can give rise to them, and it is doubtful even whether these disturbances can properly be called inflammatory. Bohn[1] and others think they are due to collateral hyperæmia and œdema, caused by embolism of small vessels in the neighborhood of the affected joints. We do not agree with them, since as yet neither the source of the emboli nor the emboli themselves have been demonstrated, and in the majority of the cases belonging in this category it would certainly be impossible to demonstrate either. It is more probable that the same structural changes in the walls of the vessels

[1] Journal für Kinderheilkunde. N. F. Bd. I. S. 391.

which are at the bottom of the disease, and which at a later period facilitate the escape of the red blood-corpuscles, and thus produce the hemorrhagic accidents, are favorable at an earlier period to the percolation of large quantities of liquor sanguinis, through the capillary walls of the most various vascular provinces in the body, and that in this way transudations take place into the cavities of the joints. When these transudations are but small in quantity, they manifest themselves only by pains, but when they are more abundant they also cause swelling. Finally, we have already stated that purpura rheumatica cannot be regarded as a hemorrhagic form of ordinary articular rheumatism, and have briefly detailed the reasons which militate against such a supposition.

With respect to the *gastro-intestinal symptoms* that are observed in many cases, we may repeat that we agree perfectly with Scheby-Buch, who regards the *bilious vomiting*, the *meteorismus* and *tenderness of the abdomen*, and also the *severe colicky* pains, as in all probability the direct consequences of the *peritoneal* irritation caused by hemorrhages into the serous coat of the stomach and intestines. These symptoms might also possibly be in part due to extensive hemorrhagic infiltrations in the mucous coat of the digestive tract. Infiltrations of smaller extent have relatively often been found in this membrane at the autopsies of purpura patients.

Nature and Pathogenesis of the Disease.

The analysis of the etiological and clinico-anatomical data shows that in morbus maculosus or purpura hemorrhagica (including the various symptomatological sub-varieties of purpura which we have here treated collectively), there exists a *transitory hemorrhagic diathesis*, which possesses, much more than other intercurrent dispositions to hemorrhage, the character of an independent, or, as we have already expressed it, of an *essential* disease. For, although, as we have shown, the tendency to extravasation is sometimes exceedingly decided and general, it is at the same time in the majority of the cases so independent of all other pathological complications, and so isolated in a

manner as a temporary abnormity of the affected individuals, that in contrast with it all other forms of the transitory hemorrhagic diathesis, and particularly the scorbutic, must be regarded as relatively very imperfect examples of this pathological species. It is evident, *à priori*, that the primary cause of this transitory, and at the same time so independent morbid disposition to extravasations from the vessels, can lie only in a disturbance of the physiological relations existing between the blood and the walls of the blood-vessels. Or, in other words, there is in morbus maculosus a primary disease, *either* of the blood *or* of the walls of the blood-vessels, or *of both together*. In consequence of the negative results furnished by the examinations of the blood in genuine cases of the disease that have hitherto been undertaken, and of the absence of all macroscopic changes in the walls of the blood-vessels, and finally, of the obscurity and confusion of the etiological conditions under which the hemorrhagic diathesis not infrequently develops in concreto almost instantaneously, to disappear again completely after a more or less prolonged existence — it is at present absolutely impossible to determine whether the mode of development in cases symptomatically identical is really always the same. Hence, simple as is the mere clinical fact of the existence in morbus maculosus of a transitory and essential hemorrhagic diathesis, and easy, as it consequently is, to define briefly and concisely the *nature* of the disease, it is in an equal degree difficult, and even for the present impossible, to answer the question as to its *pathogenesis*. On account particularly of this lack of a precise etiology and of a satisfactory histological and chemical foundation, we must always bear in mind the possibility that these cases, which resemble one another so closely in their clinical histories, may have had entirely *different* developmental histories.

The genesis of the disease appears to us relatively most comprehensible in those not infrequent cases where it occurs as an *actual sequel* to other severe and prostrating pathological processes, that is, when it is developed *not during* the existence nor *immediately after* the termination of the latter, but *at a somewhat more advanced period of the convalescence.* It is certainly possible that the intercurrent appearance of the hemorrhagic

diathesis in such cases has some connection with the very peculiar and *exceptional relations which frequently exist at that very time, between the volume of the blood on the one hand and the resisting power of the vascular apparatus on the other.* For reasons which were given in detail, when speaking of *anæmic marasmus* (comp. Vol. XVI.), it must be admitted, as probable at least, that the general nutrition and functional power of all the tissues suffer, during the course of severe diseases, in direct proportion to the impairment in the composition of the blood, and that the walls of the blood-vessels, and particularly those of the capillaries, are involved in this nutritive and functional decadence. As a result, the capillary walls become more brittle and more permeable. This condition, in itself and at first, merely predisposes to hemorrhages; but when it has reached higher grades of development, and especially when auxiliary exciting causes are present, it may lead to hemorrhages even *during* the course of the severe primary affection. Two questions now present themselves, viz.: why this hemorrhagic diathesis does *not* manifest itself more frequently as a symptomatic affection during *the course* of the primary diseases which beget it? and why, on the other hand, it should occur relatively as often during convalescence in a more *independent* manner and as a *sequel?* In our opinion the correct answer to the former question is, that the great diminution in the force of the heart's action and the marked decrease in the volume of the blood, which occur so commonly in the course of severe pathological processes, present an obstacle to the actual outbreak of the hemorrhagic diathesis which is sufficient to keep it perfectly latent in very many cases. In the same way in the normal course of convalescence, the recovery of the cardiac power and the increase in the volumes of the general nutritive fluids produced by the assimilation of new albuminous material, go hand in hand with the restitution of the functional and nutritive integrity of the capillary walls, so that at no phase of this process is there any marked disproportion between the increasing cardiac energy and the increasing mass of the blood on the one hand, and the increasing resistance of the capillary walls on the other. *If, however, during the course of convalescence from a severe disease, the restitution of the walls of the*

vessels does not keep pace with the regeneration of the blood-mass and the increase in the energy of the heart's action, it is evident that we must regard this *want of harmony* between the usually synchronous *processes of recovery* as a predisposing cause of the development of a transitory hemorrhagic diathesis. We believe in fact that the not infrequent appearance of morbus maculosus, during convalescence from typhoid fever and other severe diseases, is to be accounted for in this way. This opinion is supported by the fact that in such cases the outbreak of the hemorrhagic diathesis frequently appears immediately after some unusual movement, etc., which causes temporary excitement of the heart's action: as an instance we may mention the first attempt to stand up and walk about.

This explanation, however, is applicable only to those cases in which the purpura hæmorrhagica is developed during convalescence from some severe disease. Such cases, however, constitute only a small minority of the whole. We must here again call attention to the fact that the disease often attacks without any apparent cause individuals who were previously in perfect health. In such cases we cannot, of course, speak of a precedent diminution in the volume of the blood, nor of an alteration in the walls of the blood-vessels dependent upon anæmia, nor of a want of harmony in the regenerative processes. Here the pathogenesis is evidently different, and we may add at once that it is as yet entirely inexplicable. The examination of the blood has shown that there is no gross, palpable anomaly of that fluid which can be regarded as the cause of the supposed alteration in the walls of the vessels. Hence, in the search after an *à priori* explanation, we are driven either to assume the existence of imperceptible changes in the blood, *ex. gr.*, the importation of a deleterious, miasmatic principle, or to recognize as the basis of the hemorrhagic diathesis a peculiar disease of the blood-vessels more or less independent of the condition of the blood. Opposed to the theory of the miasmatic origin of morbus maculosus is the fact that the disease is neither epidemic nor endemic, but that the overwhelming majority of the cases are perfectly isolated. A microscopically demonstrable primary disease of the walls of the blood-vessels, at least in the rapidly fatal cases, does

not appear to exist (comp. Complications and Sequelæ). It cannot therefore be assumed in explanation of the phenomena. The theory of a *neurotic* disease of the vessels has been suggested by some recent experiments performed by Nothnagel[1] on animals, which prove that multiple hemorrhages occur in the lungs after slight lesions of certain points in the cortex of the brain. This theory is perhaps more tenable than the others. We will refrain, however, from further speculations regarding the pathogenesis of the apparently spontaneous cases of morbus maculosus. Since we cannot explain them satisfactorily, we prefer to wait till further investigations and anatomical observations shall have thrown more light upon this very obscure subject.

Complications and Sequelæ.

A particularly important and very frequent *complication* of morbus maculosus is the *acute anæmia* which is developed in severe cases as a result of the hemorrhages, and which, provided the disease does not end fatally, persists for a time after the hemorrhagic diathesis has disappeared. Of very slight prognostic importance, but still interesting, is the development of cutaneous wheals or *urticaria* which has been observed by some authors. This complication appears to occur chiefly in those cases which present severe gastric symptoms (Henoch[2] and Scheby-Buch[3]). Starting from the fact that urticaria usually occurs in connection with disturbances of the digestive apparatus, Scheby-Buch has suggested that in these cases it may be more directly dependent on the gastric disturbances than on the hemorrhagic diathesis. A fortunately very rare complication and sequel of severe cases of purpura is the *mortification and ulceration of the mucous coat of the intestines*, sometimes produced by widespread and multiple hemorrhagic infiltrations. This has been observed and described by Reumont, Hérard, O. Weber, E. Wagner, and others. The intestinal ulcers produced in this manner showed no tendency to healing, and induced

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[1] Centralblatt für die med. Wissensch. 1874. Nr. 14.

[2] l. c. p. 403.

[3] l. c. p. 490 sqq.

profuse diarrhœa, which subsequently in all the cases proved fatal through exhaustion. Zimmerman [1] reports a case of morbus maculosus Werlhofii of long standing, in which death was due to perforative peritonitis, the result of multiple eschars in the intestinal walls, which penetrated as far as the serous coat. The walls of the smallest arteries in the neighborhood of the necrotic places in this case were found on microscopic examination to be thickened in a peculiar manner. The increase in thickness affected particularly the adventitia, which was filled with countless rounded cells and nuclei. Zimmermann, after describing these appearances, refers to the peculiar cases of "Periarteritis nodosa" reported by Kussmaul and Mayer,[2] and calls attention to the resemblances as well as the great discrepancies existing between their cases and his. We readily admit that the differences in the clinical histories and the post-mortem appearances are too great to warrant us in employing the periarteritis nodosa discovered by Kussmaul and Mayer as a basis on which to build up a theory of the hemorrhagic diathesis present in morbus maculosus Werlhofii.

Diagnosis.

Since *the morbus maculosus Werlhofii*, as a clinically distinct disease, possesses a marked hemorrhagic character, it can be confounded only with such *other* processes and conditions as possess likewise a hemorrhagic habitus. For instance, it may be, and in fact often has been, confounded with *scurvy;* also, but less frequently, with the congenital and habitual predisposition to hemorrhages which characterizes *hæmophilia.* The differential diagnosis from *leukæmia* and *pseudo-leukæmia*, and from *progressive pernicious anæmia*, may also present difficulties. Finally, we must also mention the possibility of confounding it with the *symptomatic hemorrhagic diathesis* which sometimes accompanies or complicates various severe morbid processes.

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[1] Archiv der Heilkunde. Bd. XV. (1874). S. 167.

[2] Deutsches Archiv für klin. Med. Bd. I. (1866). S. 484.

The diagnostic points between *morbus maculosus* and *scurvy* are derived both from the etiology and the symptomatology of the two affections. This duplication of the differential points makes the recognition of typical cases of one or the other disease perfectly easy and certain; it is, moreover, invaluable in the more doubtful cases, since either the etiological or the symptomatic differences are separately sufficient for the differential diagnosis. Scurvy is a hemorrhagic affection which is almost without exception developed only under the influence of long and severe privation, and which, moreover, as a rule, prevails as an endemic or epidemic disease. Its development is almost never an "apparently spontaneous one," and isolated cases of the disease are relatively very rare. Morbus maculosus, on the other hand, as a rule, occurs sporadically, and in very many of the cases the disease is "apparently spontaneous." In those other cases where the anamnesis shows that the hygienic conditions with regard to habitation, food, etc., have not been good, the fact that the disease has attacked only one individual will weigh heavy in the balance against scurvy, provided it can be shown that many persons were exposed to the same unhealthful surroundings as the patient, without being similarly affected. These etiological differences are supplemented by not less important symptomatic differences, which prove of very great value in the diagnosis of doubtful cases. In the first place, the majority of cases of scurvy are preceded by a distinct and protracted stadium prodromorum. During this time usually no hemorrhages occur, but a marked general cachexia with peculiar characteristics is developed. The hemorrhagic diathesis of morbus maculosus, on the contrary, generally appears suddenly and without warning, or at most, after a very short prodromal indisposition. In none of the cases, at least in the beginning, is there anything like the scorbutic cachexia with its signs of an intense *primary* depravation of the general nutrition, which is for the most part independent of any hemorrhagic attacks. It is true that great impairment of the general health and of the bodily powers may be developed in the course of severe cases of morbus maculosus, but it is then entirely of a *secondary* and *anæmic* character, and its degree is dependent

upon the frequency and copiousness of the hemorrhages. Finally, there are also some striking differences in the character of the hemorrhagic symptoms in the two diseases. In the first place, the hemorrhagic inflammation of the gums, which is so characteristic of scurvy, is wanting in morbus maculosus, although in the latter, simple non-inflammatory hemorrhages from the gums are not infrequent. Moreover, the local symptoms in general of scurvy possess not only a hemorrhagic, but also an inflammatory character, which in morbus maculosus is either entirely wanting, or present only to a very limited extent. Further, these inflammations in scurvy show a great tendency to end in ulceration and mortification of the tissues affected. Even after all that has here been said, it might still with some appearance of reason be asserted, that between scurvy and morbus maculosus there exists only a quantitative distinction; that the former is merely a more severe, and the latter a milder form of one and the same general disease, and that consequently it is superfluous to speak of a differential diagnosis between the two. Opposed to this view, however, is the interesting fact that certain severe hemorrhagic accidents, particularly the exhausting and often fatal bleeding from the nose, stomach, intestines, urinary passages, and female genital apparatus, are much more frequent in morbus maculosus than in scurvy, while, on the contrary, the equally dangerous hemorrhages into the pleura and pericardium are more frequent in the latter. Hence, it is not so easy, on account of this very difference in the topographical distribution of the most frequent varieties of the hemorrhage, to discuss the differences in the *intensity* of the two processes. We must, on the contrary, admit, whether we wish to or not, that they differ in *quality* with regard to the symptoms as well.

Well-marked cases of *morbus maculosus* cannot easily be mistaken for *hæmophilia*, since we include in the former disease only those cases in which the hemorrhagic diathesis does not depend on an inherited predisposition, and does not constitute an habitual pathological condition, but in which, on the contrary, it is developed in an isolated manner, and is, as a rule, of a transitory nature. The following additional points of difference between the two affections may also be mentioned: the somewhat

greater frequency of morbus maculosus in the female is contrasted with the decided predilection of hæmophilia for the male sex; the usually trivial results of slight injuries in morbus maculosus as compared with the great danger attending even the very smallest wounds in hæmophilia; finally, the absence in purpura hæmorrhagica of all those symptoms of an habitual fluxionary diathesis and plethora, which seem to be rarely wanting in hæmophilia and are particularly marked just before the occurrence of the spontaneous hemorrhages. In general, therefore, it is not difficult to determine whether a given case of the hemorrhagic diathesis belongs in the category of morbus maculosus or of hæmophilia. It must not be forgotten, however, that there are also rudimentary forms of hæmophilia which remain latent during the greater part of life, and only manifest themselves transitorily, perhaps only once, perhaps oftener. Such cases, on account of this anomalous behavior, simulate morbus maculosus pretty closely. The most important diagnostic point in all such cases of hæmophilia is furnished by the fact that the hemorrhagic diathesis in question, although it appears *in concreto* to be only a transitory affection, occurs within the consanguineous circle of a bleeder family, other members of which have suffered from the more developed forms of hæmophilia. Where this criterion is wanting, we may confidently exclude hæmophilia, and diagnosticate a simple transitory hemorrhagic diathesis (morbus maculosus Werlhofii). On the other hand, morbus maculosus has been known in many cases to recur frequently throughout the entire life of an individual (Rohlfs).[1] Behavior like this indicates a special and probably congenital tendency to hemorrhagic accidents, and is very suggestive of genuine hæmophilia. But even under such circumstances no man would henceforth be excusable in making a diagnosis of true bleeder disease, unless the proof of the hereditary nature of the disease, particularly its indirect transmission from the side of the mother, can be adduced. To make the diagnosis certain, the patient should be of the male sex, and finally, it must be shown that during his free intervals, any acci-

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[1] Memorabilien. Bd. XX. S. 433 (1875).

dental traumatic hemorrhages prove exceptionally intractable. If these signs are not present, and there is no question of the possible existence of other processes, the case in question must be considered one of morbus maculosus, and not of hæmophilia.

Morbus maculosus may be distinguished from the *hemorrhagic diathesis of leukæmia* and *pseudo-leukæmia* by an examination of the spleen and lymphatic glands, and (in leukæmia) also of the blood. More difficult, and in fact only possible with the help of the microscopic analysis of the blood during life and of the examination of the medulla of the bones after death, is the differential diagnosis between simple morbus maculosus and *myelogenic leukæmia*, in those cases of the latter affection in which the spleen and lymphatic glands do not participate to any marked extent in the hyperplasia of the medulla of the bones. As an example of this we may refer to a case from the clinic at Basel, the history of which was, for diagnostic reasons, briefly detailed in the chapter on Progressive Pernicious Anæmia. This case was admitted with a diagnosis of morbus maculosus Werlhofii, and was at first regarded by us as progressive pernicious anæmia, but it was afterwards shown to be neither the one nor the other, but a subacute myelogenic leukæmia. This was positively proved, even during the lifetime of the patient, by the examination of the blood. Similar cases have probably often occurred, and been wrongly diagnosed as cases merely of *severe* morbus maculosus with fatal termination.

The diagnostic separation of *progressive pernicious anæmia* from *morbus maculosus*, is in our opinion of special importance, because we are convinced that the casuistic literature of the latter disease includes many cases which should properly be classed as progressive pernicious anæmia, and not as Werlhof's disease. An important and actually cardinal differential point in this case is that in *progressive anæmia* the *hemorrhagic diathesis* is always developed on the basis of a pre-existing, plainly evident, and very marked poverty of blood, and is consequently *secondary;* while, on the contrary, in *morbus maculosus* the *hemorrhagic diathesis* is *primary*, and the anæmia which subsequently appears in the severer forms of the disease is secondary to it. When in a given case, which presents a

marked degree of oligæmia in addition to petechiæ and other hemorrhagic symptoms, we have by exclusion narrowed the question of diagnosis down to progressive anæmia and Werlhof's disease, it is in our opinion only necessary, in order to decide the question, to ascertain the *chronological order in which the principal symptoms* presented themselves, or, in other words, to determine accurately from the anamnesis whether the hemorrhagic diathesis or the extreme anæmia was the first to appear.

The confounding of *morbus maculosus* with *symptomatic predispositions to hemorrhage* of other kinds than the above is neither theoretically excusable, nor indeed likely to occur often in practice; for the existence of some severe primary disease in connection with the latter can almost always be established without much difficulty by the demonstration of the local and general symptoms produced by it. When the examination of the patient has been conducted with proper care, and sufficient attention has been paid to the etiological conditions, it is almost invariably possible to decide, without hesitation, whether the hemorrhagic diathesis in question is only symptomatic, or constitutes an essential disease which can properly be called morbus maculos

Duration, Terminations, and Prognosis.

Even if we except the fatal cases, which sometimes run a very rapid course, the *duration* of morbus maculosus is, as a rule, short. In the majority of the cases it lasts only from two to four weeks. This includes also the duration of the consecutive anæmia, when it is not very extreme. The duration of the hemorrhagic diathesis itself is often much shorter, say from five to fourteen days. In many cases, however, the disease is more protracted, in consequence of repeated relapses of the petechial eruptions and the internal hemorrhages, or on account of the intense grade and slow disappearance of the consecutive anæmia. Many weeks and even months may then pass by before the patient is completely restored to health and the last traces of the disease have disappeared. In the majority of the cases

the disease *terminates* more or less rapidly *in recovery.* In some very rare cases it is followed by *sequelæ*, and finally not a few of the cases end *fatally.* Death is due to acute anæmia, and generally at the acme of the disease. The danger of its occurrence increases in direct proportion to the profusion and number of the hemorrhages, and to the individual intolerance of the patient to loss of blood.

The *prognosis* depends upon the grade of the disease and the bodily constitution of the patient. It is in general rather favorable than otherwise. It must not be forgotten, however, that cases which were at first very mild and apparently harmless, sometimes very rapidly change their character and become malignant. This happens when the hemorrhages, which have previously been slight, suddenly and usually without any known cause become dangerously copious and at the same time begin to affect different parts of the body. The character of the disease thus becomes suddenly severe and immediately threatening. It is therefore never possible in the commencement of a case of morbus maculosus to make a positive, favorable prognosis. On the other hand, a fatal result cannot be certainly predicted, even in those severe cases where the patients are exhausted by loss of blood, and lie in a condition of the deepest prostration. For experience has taught us that even a very intensely developed hemorrhagic diathesis in this disease may disappear quickly and completely, and that the patients under such circumstances, though perhaps with the greatest difficulty, finally recover from the condition of dangerous prostration into which they had fallen. It is evident, lastly, that the prognosis in the individual cases of morbus maculosus will depend greatly on the *treatment* employed. By the employment of appropriate measures any immediate and threatening danger may often be greatly diminished, while a neglect of the proper precautions may directly hasten a fatal termination.

Treatment.

A rational *prophylaxis* against morbus maculosus Werlhofii is for the present impossible, because the causes of the disease

are as yet absolutely unknown. For the same reason we cannot with any propriety speak of the fulfilment of the *indicatio causalis*, in the strict sense of the term. It is, nevertheless, advisable in all cases of the disease to improve the hygienic surroundings of the patients, wherever they are found to be deficient or bad. Among the lower classes, who are in general badly housed, badly clothed, and badly nourished, this is best accomplished by promptly placing the patients in well-regulated hospitals. When, on the contrary—and this is just as often the case in this disease—the surroundings of the patients are all that can be desired, the efforts of the physician, aside from the maintenance of this favorable state of affairs, must necessarily be confined to fulfilling the *indicatio morbi*, to the *symptomatic* treatment of the case.

The *indicatio morbi* calls for measures directed against the existing hemorrhagic disposition. Upon this point clearer and more reliable therapeutical rules could be laid down if more were known concerning the nature of those anatomical and functional anomalies in the vascular apparatus or the blood, which are the cause of the hemorrhages in each individual case. Since we are so much in the dark in these particulars, the measures which are usually adopted in the essential treatment of the disease must be regarded as empirical rather than rational in their nature. Above all, it appears to us dangerous to prescribe for all cases the same dietetic and medicinal regimen, based upon some positive, preconceived opinion. It is, in fact, dangerous to give others any positive directions about the treatment to be followed. This applies particularly to the practice of *venesection* and local blood-letting, which was formerly, and has been to some extent even recently recommended, especially by English and Italian physicians, on the ground that morbus maculosus depends upon a fluxionary diathesis. Clinical experience has convinced us that this, if true at all, can be so only exceptionally. In the great majority of cases, the entire behavior of the patients at the time of the outbreak of the diathesis speaks against such a supposition. The patients are liable to be called on during the course of the disease to stand the loss of a great deal of blood, and, moreover, are frequently of a habitus that

does not bear bloodletting; hence, it is certainly inadvisable to resort with undue zeal to venesection, leeches, etc., which would reduce them at once to an anæmic condition. Less dangerous, but still of doubtful therapeutic value, is the internal administration of the *mineral acids*, and particularly of sulphuric acid, in the form of the elixir acidum Halleri, which, since it was first recommended by Werlhof, has enjoyed a certain, but probably wholly undeserved reputation in the treatment of morbus maculosus. The mineral acids, with sulphuric acid at their head, are said to prove useful when administered internally, not only as hemostatics against actually existing hemorrhages, but also against the *tendency* to hemorrhage; or, in other words, against the presumptive disease of the blood and the blood-vessels. For ourselves, we must say that in the hemorrhagic diathesis in general, and in morbus maculosus in particular, we have never seen any noticeable results from the administration of sulphuric or of any other of the mineral acids (nitric, phosphoric, muriatic) in their usual forms and doses. We cannot, consequently, join in the praises which others lavish on them. The *vegetable acids* (acidum aceticum, tartaricum, citricum) seem to be even less efficacious. They have been repeatedly tried in morbus maculosus, but with the same negative results as in scurvy. It is an interesting fact that the use of a *fresh vegetable diet*, which is usually so beneficial in the treatment of scurvy, has been proved to be utterly ineffective against morbus maculosus (Curran and others). This is another argument against the identity of the two diseases. Mignot, Argaing, and Loufflet state they have obtained good results from the internal administration of the *solution of chloride of iron* in doses of one to five drops every two hours, in a mucilaginous vehicle. Other authors recommend *ergot*, and others still *acetate of lead* in half-grain doses, several times a day. Our own personal observations, however, have convinced us that none of the above-named remedies, except perhaps the last, exerts any influence worthy of mention on the hemorrhagic diathesis in cases of morbus maculosus. Even the efficacy of lead seems to us as yet rather problematical. Respecting the value of *oil of turpentine*, formerly recommended by Neligan, Sewruch, Curran, and others, we have

no recent observations. Since, therefore, there is no special medication which can be recommended as reliable, the occurrence of the hemorrhages must be guarded against as far as possible by a strict enforcement of *dietetic treatment.*

Here careful attention on the part of the physician is often very useful, for many hemorrhages are undoubtedly directly provoked by the non-observance on the part of the patient of a proper regimen. In the *first place,* every direct mechanical injury of the body must be guarded against, since a push, a blow, a jar, or strong pressure on any part, may cause a hemorrhage. *Secondly*, and particularly in the early stages of the disease, everything which is liable to excite the heart's action, and thus increase the internal pressure in the vessels, must be avoided. Mental and bodily rest must be strictly enjoined. The patients must not only remain in bed, but they must avoid all active movements in the bed. The sick-room should be kept cool, and the patient must not be too warmly covered. The food must be nutritious, but bland, must be taken cold, and should consist chiefly of milk. Of other drinks, except when counter-indicated for some reason, iced water and lemonade are the most suitable; they may be given in small quantities as often as the thirst may demand. On the other hand, the ingestion of large quantities, even of the above-named kinds, must be prohibited decidedly, since the entrance of large quantities of fluid into the blood may induce a transitory condition of *plethora ad vasa*, which may result in hemorrhage. Hot or even warm drinks must not be given; the same may be said in general of alcoholic spirits, although certain symptomatic indications may at times demand them. It is very desirable that the bowels should be moved regularly, since the accumulation of fæces in the intestinal canal is well known to lead to collateral fluxions in the upper part of the body — a condition favorable to the occurrence of hemorrhages. Existing constipation should be treated principally by clysmata, or at all events, by very mild cathartics (*e.g.*, oleum ricini). Drastics are positively interdicted, as they directly provoke intestinal hemorrhages, and, aside from that, often lead to a premature prostration of the strength.

The *indicatio symptomatica* demands first of all a direct

treatment of the existing hemorrhages. For the measures to be adopted against the attacks of epistaxis, hæmatemesis, hæmaturia, etc., we refer the reader to the chapters on Hæmophilia and Scurvy. We think it unnecessary in this place to add anything to the directions there laid down, except perhaps that they must be carried out with proper energy. The *articular pains and the swelling of the joints* in the so-called "purpura rheumatica" require narcotic liniments, or, if the pain be very severe, morphine internally or subcutaneously. A special treatment of these symptoms is, however, often unnecessary, as they disappear spontaneously after a short time.

It is of great importance that, during the height of the disease in severe cases, due attention should be paid to the *symptoms of the complicating acute anæmia*, which is liable to be developed sooner or later in consequence of loss of blood, and is often fraught with immediate danger to life. Moreover, after the cessation of the hemorrhages and the final disappearance of the hemorrhagic diathesis, *anæmia*, which usually remains behind, requires appropriate treatment. In regard to the first point, we refer the reader to the directions given elsewhere, and particularly to those given in connection with the treatment of hæmophilia. We will only add here that the indications for the use of *stimulants*, such as wine, champagne, cognac, and camphor, are often enough present during the course of morbus maculosus, viz., whenever the weakness is increasing, and the action of the heart threatens to cease. It is well, however, to confine the extensive use of these excitants to the occasions of actual necessity. The operation of *transfusion* does not promise much in morbus maculosus, since it cannot lessen the danger of new hemorrhages. The results of the operation, whenever it has been practised in cases of Werlhof's disease (Juergensen, Th. Smith, and others) were invariably unfavorable. The *after-treatment* of morbus maculosus, or the *removal of the residual anæmia*, requires the use of *nutritious and easily digested food*, fresh air, and other dietetic roborantia, and especially the administration of preparations of *quinine* and of *iron*, in increasing doses. It must be laid down as an absolute rule, however, that the administration of the preparations of iron should not be be-

gun till after the hemorrhagic diathesis has completely disappeared, and not until the patient has for several days been entirely free from even the slightest signs of its existence, such for instance as a fresh outbreak of petechiæ on the legs after the convalescent has been walking about for some time. The too early use of iron has in many cases evidently led to relapses of the disease. Hence, although we believe that a bold administration of iron is of the very greatest value during convalescence, we are also convinced that experience has proved it to be unadvisable, and even absolutely counterindicated, during the actual persistence of the disease.

POISONS.

BOEHM.

FIRST PART.

Poisoning by Metalloids; Acids; Alkalies, Earths, and their Salts.

FIRST DIVISION.

Poisoning by Metalloids.

CHAPTER I.

POISONING BY CHLORINE.

Notwithstanding its manifold applications in the arts as a bleaching and disinfecting agent, chlorine does not belong among the especially important substances of practical toxicology.

In most instances we have to deal with cases of poisoning by the action of free gaseous chlorine on the organs of respiration, and more rarely with cases of internal poisoning by the aqueous solution, as chlorine water or solutions of bleaching salts (alkaline hypochlorites, javelle water, Labarraque's solution), which, as well as the so-called chlorinated lime, readily afford appreciable quantities of chlorine gas. Still, in poisoning by the last-named substances, the caustic action of the alkali must also be taken into consideration.[1]

Chlorine gas is distinguished by a characteristic unpleasant smell, and by its property of strongly irritating the mucous membranes; it is of a greenish color and readily soluble in water. The peculiar chlorine odor also pertains to chlorinated lime and the hypochlorites.

The hostile relation which chlorine bears to the animal organism apparently arises from the strong affinity of this element for

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[1] Cf. Chapter on poisoning by lyes.

hydrogen, with which it forms hydrochloric acid. According to the researches of Bryk[1] in regard to the action of chlorine on animal tissues, the ammonia formed by the decomposition of the protein substances unites with the chlorine to form ammonium chloride.

Dilutions of blood and albumen are coagulated by chlorine, the former being changed into a dark brown greasy mass,—hydrochloric acid, according to Eulenberg,[2] being formed at the same time.

The question whether the action of chlorine is to be regarded essentially only as a local irritant and caustic, a view which has been entertained by Hermann,[3] or whether, besides the local irritation, a more constitutional action must be assumed, cannot yet be settled with certainty.

The possibility of the existence of free chlorine in the blood has been very properly rejected by Hermann, and we can now only question whether the hydrochloric acid or other combinations, as yet unknown, which the chlorine forms in the blood or before entering into it, exercise a constitutional action. The paralysis of the heart, observed in animals in consequence of the action of chlorine, is brought up by F. Falk[4] as a positive indication that the chlorine is changed to hydrochloric acid, since it is well known that the acids paralyze the hearts of frogs. The disturbances of nutrition, observed among workmen who have been exposed for some time to the influence of chlorine fumes, might also perhaps be considered by some as confirming the above idea of a constitutional effect produced by chlorine. In all this, however, we are still confined to the domain of pure hypothesis so long as the change from chlorine to hydrochloric acid in the blood during circulation, or the absorption of hydrochloric acid, which has been formed from chlorine in the stomach and intestinal canal, has not yet been shown. Accurate examinations of the urine would soon settle this point, since evidently such an appreciable addition of hydrochloric acid would dimin-

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[1] Virchow's Archiv.

[2] Die schädlichen und giftigen Gase. S. 216.

[3] Experimentelle Toxicologie. S. 143.

[4] Vierteljahrschr. f. gerichtl. Med. v. Eulenberg. 1872. N. F. XVI.

ish the alkalies, and would, moreover, cause an increased elimination of chlorides.

Eulenberg thinks that the blood-corpuscles, under the action of chlorine, lose their capacity for respiratory changes by the decomposition of the coloring matter which they contain. This might happen if the two should come directly into contact with each other. Falk, who was able to produce the same effects upon frogs which had been bled (through the action of salt) as upon those in a normal state, by means of chlorine, concludes from this that it is superfluous to suppose an alteration in the blood-corpuscles as the effect of the action of chlorine, and regards the result of his experiment as an indication that chlorine in itself acts as a poison upon the heart. But we cannot see why the chlorine may not be changed into hydrochloric acid in its action on these frogs which have been bled.

The fact that a decided odor of chlorine has been noticed in the brain and organs of respiration by Cameron,[1] on post-mortem examination of a person who had died from poisoning by chlorine, does not seem to us a sufficient ground for assuming that free chlorine circulated in the fluids and blood during life.

The primary effects of the poison when inhaled are, firstly, irritation of the nerves in the mucous membrane of the organs of respiration, and, secondly, certain reflex actions caused by that irritation. To the latter belongs the spasmodic closing of the glottis which in former times was generally regarded as the cause of death in chlorine poisoning. Von Hasselt and Mulder,[2] however, observed that rabbits placed by them in an atmosphere of chlorine gas did not perish from spasm of the glottis, but breathed the gas for some time. Recently F. Falk confirmed this observation, and further noted that the closing of the glottis on inhalation of chlorine lasted but a very short time, and the animal before succumbing drew several deep breaths with the glottis open. He further found that the spasm of the glottis is a reflex action brought into play by sensible irritation of the nerves of the larynx itself, or of that portion of the air-passages which is situated above it, for it does not take place if the

[1] Dubl. Quart. Journ. 1870. Cf. *Hirt*, Krankheiten der Arbeiter. I.

[2] von Hasselt-Henkel's Toxicology. II.

animal is made to inhale the gas through a tracheal fistula below the larynx.

The disorders resulting from the introduction of solutions containing chlorine into the digestive tract are of a gastro-intestinal nature.

Besides chemists and apothecaries, who occasionally, through lack of skill or by mischance, poison themselves with chlorine fumes, workmen in certain chemical works (as chlorinated lime works and bleacheries) are especially exposed to the prolonged influence of larger or smaller amounts of the gas. But all authors agree in this, that the evil effect on the health thereby caused, aside from some chronic affections to be described farther on, is not very decided, and that the workmen may live to an advanced age.

It is only in rare instances that chlorine-poisoning has taken place in any other way than those already mentioned, and these cases were almost all brought about through accident. In the literature of the subject we have found a single instance communicated by Barbet,[1] in which a man committed suicide by taking javelle water (sodic hypochlorite).[2]

Injudicious disinfection of sick-rooms by chlorinated lime may under some circumstances also cause poisoning. Halfort[3] has reported cases of illness caused in this way, and also remarks that during a cholera epidemic some of the post-office officials, whose duty it was to disinfect the letters, contracted phthisis in the performance of this duty. Up to the present time eleven cases of acute poisoning by chlorine have been recorded in the literature, five of which were observed by von Hasselt, two by Dieudonné, and one each by Mulder, Henkel,[4] Simonson,[5] and Cameron (l. c.); the case recorded by Simonson was the only one ending in recovery, the others being fatal. Under the head of Poisoning by Lyes, we have considered the

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[1] Journ. de méd. de Bordeaux. 1843.

[2] Javelle water is *potassic* hypochlorite. The sodic salt is known as Labarraque's solution.—TRANSLATOR.

[3] Krankheiten der Arbeiter und Gewerbtreibenden. Berlin, 1845.

[4] von Hasselt-Henkel. Toxicologie. II.

[5] *Casper*, Wochenschr. 1837.

cases which Tardieu[1] has reported of poisoning caused by bleaching fluids.

As regards the amount of chlorine necessary to cause poisoning, the fatal dose, etc., as may be readily understood, no specific data can be given. The more concentrated the atmosphere of chlorine, the more powerful the action. The fact, however, should be noted that the organism appears to accustom itself to the effects of moderate amounts of chlorine. Workmen in the above-mentioned establishments can live without discomfort in an atmosphere which causes severe irritation in those unaccustomed to it.

The symptoms of acute chlorine-poisoning in human subjects consist at first in severe reflex phenomena: violent coughing, sneezing, flow of tears, sharp pains in the thorax, and dyspnœa. Moreover, after leaving the poisonous atmosphere these phenomena persist for some hours with varying intensity.

If the poison acts for a longer time, more serious affections of the organs of respiration ensue, consisting in spitting of blood, difficult respiration, temporary spasms of the glottis, and a pneumonia which usually ends speedily in death. Vomiting has been noted in several cases.

What particular phenomena precede death in very acute poisoning have not been clinically established.

The statement, that workmen exposed for some time to chlorine fumes are predisposed to phthisis, has been absolutely denied by all recent authors. But almost all the persons affected lose flesh perceptibly, though they are not incapacitated for work thereby; the face shows an unhealthy color, and they suffer from mild catarrh of the stomach and chronic bronchitis. In almost all cases the acuteness of the sense of smell is also diminished (Hirt). Moreover, the frequently proclaimed immunity of the workmen in question from cholera and other epidemic diseases,[2] is, according to Hirt, not an invariable rule.

Regarding the lesions found after death in cases of chlorine-poisoning, we possess but little information. Cameron observed

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[1] Étude médico-légal sur l'empoisonnement. 2. Edit. Paris, 1875.

[2] *Christison*, Treatise on Poisons.

congested lungs, the bronchi filled with a bloody fluid, and inflammation of the trachea.

As antidotes to chlorine-poisoning most hand-books recommend inhalations of hydrosulphuric acid or ammonia. In the first case hydrochloric acid and water [? TRANS.] are formed, in the latter ammonium chloride.

These agents under the most favorable circumstances can evidently only render the chlorine still in the air-passages harmless, while they would only increase the irritation at the time of inspiration, but never remove it. But since the first result may be attained by simple removal from the agent which causes the difficulty, we would not recommend these antidotes to any one. Breathing hot vapor of water is apparently much better. For the distressing spasmodic coughing, Hirt recommends inhalations of chloroform. The deleterious effects of chlorine fumes, as Bolley [1] recently stated, may be quickly removed by inhaling small amounts of aniline. But whether this agent is suitable for the treatment of more serious cases of chlorine-poisoning, has not yet been determined.

However, in most cases the most important thing is a judicious treatment of the symptoms, and we scarcely need make any further statement than that detailed rules cannot be laid down.

CHAPTER II.

POISONING BY IODINE (TINCTURE OF IODINE AND POTASSIUM IODIDE.) IODISM.

Iodine and potassium iodide, as well as the corresponding bromine preparations, first assumed importance in practical toxicology when they were introduced into the pharmacopœia, and in their action on the animal organism the iodine preparations present numerous analogies with those of bromine. But, while during the last few years numerous treatises have appeared on the action of bromine, researches on the pharmaceu-

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[1] Zeitschr. f. Hygiene. I. 1.

tical and toxicological action of iodine, aside from its relations to absorption and elimination, are surprisingly few in number.

Iodine, though volatile like bromine and chlorine, is far less active when in the gaseous state than they. Since its boiling-point is very high (180° C.), its violet vapors are liberated very sparingly at ordinary temperatures, and consequently exert a far less intense irritation upon animal organisms. The ordinary forms in which this substance acts poisonously are the alcoholic solution of iodine (tincture of iodine) and potassium iodide. Although these two preparations are chemically very different from one another, inasmuch as the one affords an element endowed with strong affinities, while the other is an entirely indifferent salt, yet they so far agree in their action, that the potassium iodide in the organism undoubtedly may have the specific effect of iodine. Their action on animal organisms only differs to this extent, in that the potassium iodide has not the active local action which gives the iodine tincture a place in the category of corrosive poisons.

The alcoholic solution of iodine, as well as the aqueous solution of potassium iodide, is readily taken up by the fluids of the body, when applied to a mucous surface, to the subcutaneous cellular tissue, or to a serous surface. Tincture of iodine and potassium iodide (the latter in the form of iodine ointment) readily pass into the blood from the external skin, while aqueous solutions of potassium iodide, like solutions of salts in general, under ordinary conditions are not absorbed.

Roussin,[1] who has made a careful study of this point, found that absorption took place through the cutis, when he allowed the solution to dry on the skin, when the body was sprinkled with pulverized potassium iodide, or when a shirt impregnated with the powder was worn. From this it appears as if the secretions of the skin, under these circumstances, favored the process of absorption, while in the presence of water their semi-fatty nature interposed an obstacle to the penetration of solutions of salts into the sebaceous and sudoriferous glands.

Numerous observations have been made on the mode and the form[2] in which the iodine preparations are eliminated. According-

[1] Rec. de mémoires de méd., etc. milit. 3. Ser. XVIII. p 134.

[2] *Claude Bernard*, Arch. géner. 1853. I.; *Lehmann*, Physiol. Chemie; *Strauch*, Inaug.-Diss. Dorpat, 1852; *Heubel*, Inaug.-Diss. Dorpat, 1865; *Lehwald*, Abhandlun-

ing to these, they first appear in the saliva, combined with an alkali (as a rule, sodium), in from one and a half to ten minutes after they have been taken; then, after some hours, in the urine, in the gastric juice, in the bile, and in the milk. Much the largest proportion of the iodine leaves the organism within twenty-four hours by way of the urine; a small amount, however, remains in the body for some time (even for several weeks), and appears, according to the researches of Cl. Bernard and Heubel, to go through a sort of cycle, inasmuch as the salt eliminated in the saliva and stomach is reabsorbed in the intestinal canal, and the substance is only gradually eliminated in small quantities at a time by the kidneys. Iodine was also detected for several days in the milk of women who were suckling infants several days after it had disappeared from the urine.[1]

In a case reported by Rose,[1] in which large quantities of tincture of iodine were injected into a large ovarian cyst after emptying it, the major part of the iodine was eliminated by the mucous membrane of the stomach, which Rose consequently considers as the especial organ for the elimination of iodine. In this case, which unfortunately stands alone, the woman was in other respects healthy.

It is, moreover, especially striking that free iodine should make its appearance on the mucous membrane of the stomach, as was shown by Rose in the following manner: the stomach, on being laid bare at the autopsy, presented a brown color, which soon disappeared after it had been exposed to the air.

The question as to how iodine and potassium iodide act in the organism has been much discussed. The fact that free iodine is never found in the urine or any other secretion (with the exception of the single case quoted above from Rose), but always some salt of hydriodic acid, leads to the inference that the free iodine in the tincture always exerts its affinity for hydrogen in the organism, and must combine with an alkali. Whether it enters first by substitution into the tissues, perhaps by circulating in the blood as iodine albuminate, and is then converted into an alkaline salt, or whether it simultaneously

gen der schles. Gesellsch. f. vaterländ. Cultur. Abtheil. f. Naturw. und Medicin. 1861. III.; *Roussin*, l. c.; *Melsens* (cit. Husemann), *Mor. Rosenthal* (Wien. med. Halle, 1862), and others.

[1] Virchow's Archiv. XXXV. 1866.

forms both compounds when brought into contact with the mucous coats, are still open questions.

In any case the affinity of iodine for hydrogen sufficiently accounts for its corrosive action, which differs in no respect from that of other corrosive substances. The possibility of the existence of free iodine in the blood of living animals for any length of time, is generally discredited.

But if the specific action of tincture of iodine is explained on the hypothesis that the iodine albuminate is the vehicle of action, so much greater becomes the difficulty of explaining the analogous action of potassium iodide. An entire decomposition of this salt in the stomach is not readily conceivable. When it comes in contact with the common salt there present, the two must unquestionably be changed into potassium chloride and sodium iodide, but in this latter form it would become diffused in the blood, and would finally leave the body by way of the kidneys. But since we cannot expect any action of iodine from the indifferent sodium iodide, there remain to us but two ways out of the difficulty, viz., either to deny that potassium iodide possesses any specific action of iodine—as in fact many authors have done —or to assume that the conditions are such in the body that iodine is liberated from its alkaline salts. Several observations tend to favor this last view.

While, on the one hand, Sartisson,[1] who worked under Buchheim's direction, has already in 1866 indicated the possibility that iodine may be set free from alkaline iodides by contact with certain animal secretions (saliva, nasal mucus), owing to the presence of nitrous and carbonic acids in them, quite recently Kaemmerer[2] and Binz[3] have brought forward new points of view, which tend to substantiate the assumption of a decomposition of potassium iodide in the body. Kaemmerer thinks that abundant opportunities are offered for it in the blood. In the first place, he supposes that through the agency of the carbonic acid, which is present in the blood in large quantities, hydriodic

[1] Inaug.-Diss. Dorpat, 1866.
[2] Virch. Arch. Bd. LIX. 1874.
[3] Ibid. Bd. LXII. 1874.

acid is set free[1] from the potassium iodide, with simultaneous formation of sodic bicarbonate. This acid, however, is at once decomposed by the oxygen of the blood, and iodine is set free.

Binz has established experimentally the fact that iodine may be separated from potassium iodide in aqueous solutions in the presence of carbonic acid and protoplasm. Since these very conditions are everywhere afforded in the tissues of animal organisms, Binz concludes that in those tissues an analogous decomposition of potassium iodide takes place. He therefore locates the place of this change not in the blood, as Kaemmerer does, but in the tissues (lymph-glands, muscles), and makes the point against the last-named author, that the oxygen of the blood, which is stored up in the blood-corpuscles during life, and is intended for other functions, does not possess the requisite power of oxidation to effect the dissociation of the potassium iodide. All other processes of combustion during life most probably do not take place in the blood while circulating, but in the tissues.

In the observations and discussions quoted there is an unmistakable advance, and though the question regarding the locality where the decomposition of the potassium iodide takes place, and regarding the exact mode of this decomposition in the organism, cannot as yet be definitely settled, yet the fact itself can no longer be doubted, for nobody surely will again with Boinet[2] attribute the action of potassium iodide to the potassium.

Of the general action of iodine we are but imperfectly informed. The ingenious explanations to which Kaemmerer resorts in his hypothesis regarding the separation of iodine in the blood are not founded on facts, and they take us no farther than do the theories which were current before his time, and which attribute to the iodine an influence in retarding and modifying the changes in the tissues. Von Boeck,[3] with whose treatise Kaemmerer does not appear to be acquainted, has determined by accurate quantitative estimation of the tissue-changes

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[1] That this is possible in very dilute aqueous solutions, has been shown by Struve.

[2] Gaz. hebdom. 1864. 14.

[3] Zeitschr. f. Biologie. V. 1869.

in the human subject, that the elimination of urea, during a course of treatment with iodine, suffers no change, and, therefore, that we have no right to say that iodine has any effect on the tissue-changes in the animal economy. If Kaemmerer's explanation were true, that by the separation of iodine in the blood and by the formation of the correspondingly powerful oxidizing agent, potassium peroxide, an "*increased activity in the tissue-changes and a more complete consumption of the constituents of the blood*" must take place, we would infallibly be able to detect the result of this increased action in the substances eliminated by the excretions. But this, as has been stated, is not in the least degree the case. Moreover, the argument used by Kaemmerer in support of his theory, viz., that persons who are under treatment by iodine frequently lose flesh and become anæmic, can and must, as we shall see below, receive medically quite a different interpretation.

At the same time the results obtained by Von Boeck's observations are also in direct conflict with the statements of Rabuteau[1] and Milanesi,[2] both of whom, depending on researches made on human subjects, found, not an increase—as one should expect from Kaemmerer's theory, but a very perceptible diminution in the amount of urea eliminated.[3] Since, up to the present time, Von Boeck, whose researches were made in Voit's institute, is the only experimenter who has taken every possible precaution to avoid those numerous sources of error which are inseparable from determinations of this kind (we refer especially to the control of the diet); and since, furthermore, the statements of the other two authors show a suspicious discrepancy in one particular, viz., that, notwithstanding the enormous diminution in the amount of urea excreted, they were unable to establish any increase in the weight of the body—we must, for the present at least, attach greater value to the results obtained by the first-mentioned author.

The disorders of nutrition which sometimes occur in cases of

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[1] Gaz. méd. de Paris. 1869.

[2] *Husemann*, in Virch. u. Hirsch's Jahresber. 1873.

[3] According to *Rabuteau*, this diminution was 40 per cent. (!) ; according to Milanesi, only from 4 to 19 per cent.

prolonged treatment with iodine, viz., the general loss of flesh and the complex of symptoms included under the designation of iodine cachexia, are not quite incomprehensible, even if we cannot prove experimentally some alteration in the tissue-changes.

It is well known that in such cases of protracted treatment with drugs, as a rule, after some time the organs of digestion suffer more or less. Rose found in a case of iodine-poisoning, not only during life frequently repeated vomiting, but also after death, at the autopsy, extensive degeneration of the peptic glands, through which apparently a portion of the iodine had been eliminated from the organism. Although these important results were obtained in a case of acute poisoning, and are therefore not to be forthwith utilized in explaining the more chronic disorders of nutrition which characterize iodism, yet facts are not wanting to show that also in protracted iodine-poisoning similar disorders in the functions of the stomach occur. In the by no means rare cases where, in spite of the accomplishment of the desired therapeutical effects of iodine, disorders of digestion are lacking, we usually find no loss of flesh or other cachectic phenomena. But where disorders of digestion are present at the time when the iodine treatment is begun, or develop in the course of it, they must, should the treatment last for any time, of necessity affect the general nutrition of the body, and so lead to loss of flesh. But then, without going out of our way to seek for an explanation in some mere hypothesis, we would naturally attribute this loss of flesh to the diminished amount of food taken and assimilated.

The assumption of the existence of an "iodine fever" has also strengthened very much the obscure ideas that are held by some in regard to the influence of iodine on the tissue-changes, and in regard to a febrile consumption of the vital forces by that element. But it is impossible to find in the literature of this subject reliable data for the belief in the existence of such a specific fever, unless we regard the general statements, respecting a feverish state and the like, as indicating the existence of such a fever. In cases in which the most marked symptoms of iodism were present, and in which all the indications of fever (such as flushed face, quickened pulse, etc.) were observed, Rose failed

to find the only true criterion of fever, viz., the rise in the temperature of the body. From this we are tempted to draw the inference that earlier authors were misled by the above-mentioned symptoms into believing that there was such a thing as an iodine fever.

From the general phenomena of iodine-poisoning, therefore, no information is to be gathered regarding the nature of this state. For further information regarding the other phenomena of iodism in man, the reader is referred to the Symptomatology. Meanwhile, we must here briefly consider the remaining experimental labors in regard to the action of iodine.

Experimenters have not been lacking who have conducted long series of researches on themselves, on other men, and on animals, with the different preparations of iodine. Joerg[1] and his pupils, Orfila[2] and Magendie, devoted themselves specially to researches of this kind, but they established very little of importance besides the local and corrosive action of the poison.

Magendie injected a drachm of the tincture of iodine into a vein of a dog, without thereby producing any effect. A few years ago M. Benedikt[3] also made a series of experiments on frogs, by which, however, our knowledge of the remote action of iodine was not essentially advanced. Iodine, like many other poisons, paralyzes the power of voluntary motion in frogs, and produces this effect apparently by affecting the spinal cord. Finally, Sartisson (loc. cit.) furnished evidence that the absorption of iodine by the salivary glands is determined by nerve-influence, and not by the chemical affinity of the poison for the substances of which the gland is composed.

For convenience of reference we may distinguish three categories of etiological importance in iodine-poisoning:

1. The occupation (as an ordinary workman) of preparing iodine in chemical works; 2. Accidental or intended poisoning with large amounts of tincture of iodine or Lugol's solution; and 3. The therapeutic use of iodine, which alone leads to iodism in the restricted sense of the term.

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[1] Materialien zu einer künftigen Heilmittellehr. I. Leipzig, 1825.

[2] Toxicolog. gen. I. 70.

[3] Wien. med. Zeitschr. 1862.

The pernicious effects of iodine on workmen in iodine manufactories are limited, according to a communication of Chevallier's,[1] to the moment when the iodine obtained by sublimation must be removed from the receiver. In this operation, which involves an exposure not merely to the fumes of iodine, but also to those of chlorine, the workmen, as a rule, experience a copious flow of tears, and sometimes even slight fits of coughing ; serious inconvenience and illness never occur.

Severe cases of acute poisoning arise either by the introduction of iodine preparations into the stomach, or, as has recently often happened, by the injection of large quantities of tincture of iodine or Lugol's solution into serous cavities or sacs—especially into ovarian tumors. The number of cases on record arising from the first-mentioned mode is not large. We have already referred to the two cases reported by von Hasselt and Husemann, where suicide was committed by taking tincture of iodine internally ; to these a third must be added, where (quite recently) two ounces of the tincture was taken internally.[2] If we add to these the earlier cases mentioned by Taylor (poisoning of a woman by one ounce of the tincture), Gairdner (fatal poisoning of a child by one scruple of the tincture), and Gillespie (quoted by Husemann), the number of all the recorded fatal cases of poisoning by the internal administration of iodine amounts to six.

The number of fatal cases from the injection of solutions of iodine into ovarian cysts is much larger. Velpeau records twenty, Legrand three, which came under their personal observation. Here belong also the communications of Rose, who reports one fatal case, and one followed by recovery, in his own practice, and also mentions two other fatal cases of which he accidentally heard. The entire number of those fatally poisoned is, therefore, twenty-seven—a frightfully high figure, if we consider that they are exclusively cases which have occurred as the results of medical treatment. Finally, in this category belongs also the case recorded by M. Benedikt, where fatal poisoning followed the injection of tincture of iodine into the sac of a spina bifida.

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[1] Annales d'hygiène pub. 1842.

[2] Reported by *Hermann*, of St. Petersburg, in the Petersburg med. Zeitschr. XV.

The more chronic form of what might be termed therapeutic iodism occurs chiefly after the prolonged administration of small doses of iodine or of potassium iodide; old strumous cases, and individuals who are very much run down through syphilitic cachexia, are especially predisposed to it. Aroneet[1] has collected data from the literature on the frequency of the occurrence of iodism after the use of different preparations of iodine. In the case of tincture of iodine, he found only 20 cases where the use was followed by serious effects; in 213 cases no mention was made of any injurious effects; while in 303 it was expressly stated that the drug produced no detrimental effects. The use of Lugol's solution of iodine with potassium iodide caused indications of poisoning six times, and no hurtful action in 245 cases; while from the use of potassium iodide alone Aroneet found that iodism had been produced in 40 cases. Although these different observations evidently warrant no safe conclusions, they perhaps convey a fairly correct impression of the frequency of iodism. No statistical communications on this point have been very recently made, but from the increased number of cases of iodine exanthemata observed, it may be surmised that, owing to the exclusive use of potassium iodide—for instance, in syphilis—iodism has rather increased than decreased.

It is not possible to give exact data regarding the doses of iodine which may be considered as fatally poisonous. Our knowledge on this point is comprised in the communications which we have made above. Even small amounts, if administered throughout a considerable period of time, suffice to produce iodism. In the fatal case reported by Rose, he injected into the ovarian cyst a drachm of potassium iodide, and five ounces of tincture of iodine—the amount ordinarily used in the operation—and then, after the lapse of a few minutes, removed from the cyst what remained of the fluid injected. If in washing out the cyst, however, in cases of this kind, we should neglect to do it thoroughly, very appreciable amounts of iodine may remain behind and become absorbed.

Poisoning by large quantities of tincture of iodine taken

[1] Inaug.-Dissert. Dorpat.

internally affords especially the phenomena of a severe affection of the stomach and bowels. Violent burning pains are felt in the fauces, pharynx, and along the œsophagus, as well as in the stomach and abdomen. Generally vomiting follows, though sometimes only retching and nausea. The matter vomited is more or less blue (iodine reaction), if starchy substances were present in the stomach, and possesses the characteristic odor of iodine. The stools, which are usually profuse, are also colored with iodine; at first they are of a pappy consistence, and later on bloody and slimy. At the same time there is almost always complete anuria. The general symptoms here described are identical with those observed in cases of poisoning by injection of solutions of iodine into ovarian cysts. To avoid repetition, we will here omit them. Death from internal poisoning by tincture of iodine may ensue within thirty-six hours, though of course much depends upon the amount of iodine contained in the dose.

Poisoning after the injection of large quantities of iodine into ovarian cysts affords us an opportunity of observing the constitutional symptoms which are produced by large doses of this substance, without the disturbing influence of local symptoms; for experience shows that the phenomena of peritonitis occur but seldom under these circumstances.

The injection itself is sometimes accompanied or immediately followed by violent pains, which in sensitive persons may constitute so prominent a symptom as to overshadow all others, and under some circumstances may cause swooning. Next, in the course of a few hours after the operation, a state of excessive weakness and apathy, with increasing paleness of the face, cyanosis of the visible mucous membranes, and coldness in the extremities, is developed. The pulse, which grows steadily weaker and soon disappears entirely at the wrist, becomes exceedingly rapid (170 beats per minute, and more); when the effects of the poison are at their height, it is only perceptible in the arteries near the heart, although the heart-sounds are forcible, and even increased in intensity. Within the first twenty-four hours these symptoms reach their maximum. Severe nervous symptoms are observed neither in the cases of poisoning by the stomach, nor in those of poisoning by injection; but there

is frequently repeated and painless vomiting of a copious watery fluid, which appears on the scene pretty early. This vomiting is provoked by every attempt to take nourishment, but the very intense thirst can be more easily assuaged without such consequences. The stools are sometimes diarrhœic. The secretion of urine is usually also entirely suppressed.

If the patient survive this stage, the paleness of the skin gives place on the second or third day to a deep flush, which is quite as striking in appearance. The temperature rises to the normal level, without overstepping it, and the pulse gradually diminishes in rapidity, and becomes again perceptible at the extremities. The vomiting persists, but the kidneys now begin to excrete a slightly albuminous urine. In the course of the next few days the characteristic exanthem, the angina, and the coryza show themselves. In the single case published by Rose, which, together with the case reported by Hermann, constitutes the sole basis for the present description, death ensued suddenly and without the least warning, on the tenth day—probably from paralysis of the heart.

It is evident that the very limited casuistical basis for this clinical description can permit only a very cautious generalization. Still, Rose's observation is the more worthy of attention, since in its essential symptoms it presents a striking coincidence with the case of internal poisoning described by Hermann. In the latter, too, the characteristic disturbances of the circulation were very marked, and although the vomiting must perhaps be ascribed more to the local irritation of the stomach caused by the tincture, the complete absence of nervous symptoms was as noticeable as in Rose's case. The suppression of the urine was also the same in both cases.

Rose, on the ground of his own observations, assumes the pathognomonic effect of poisoning by iodine to be a prolonged arterial spasm which produces the suppression of urine as well as the symptoms of paleness, weakness of the pulse, and coldness. Naturally such a universal contraction of the arterial system presents an obstacle to the circulation of the blood which forces the heart to excessive exertion—hence the exceedingly quick pulse (by irritation of the accelerating fibres ?). In Rose's

own case it finally led to paralysis of that organ. The cessation of this spasm is followed by excessive reddening of the skin and the relative rise in temperature, phenomena which probably led to the erroneous assumption of an iodine fever.

The vomiting, which persists throughout the entire course of the symptoms, and is accompanied by pretty intense sensitiveness to pressure over the region of the stomach, is ascribed by Rose to the material alterations in the mucous membrane of the stomach, which are excited, as has been already stated, by the elimination of the iodine through the peptic glands.

Before entering upon the description of those cases of poisoning which are due to the internal use of the preparations of iodine in small quantities, we must mention the fact, that sometimes individuals, after taking a single moderate dose, suffer from symptoms of poisoning (vomiting, diarrhœa, etc.), which are quite out of proportion to the amount taken. We meet still more frequently in practice with cases in which the first doses of potassium iodide produce moderately severe nervous symptoms, such as dizziness, palpitation of the heart, headache, and slight convulsive movements. It was probably cases like these which gave rise to the not very appropriate term "ivresse iodique," which is employed in France.

The morbid phenomena which arise from a prolonged use of small doses of iodine or of potassium iodide, and are ordinarily comprised under the term *iodism*, consist of several groups of symptoms, which sometimes occur all together, and sometimes separately. That these symptoms do not exclusively belong to chronic iodism is sufficiently shown by Rose's case. We find them also in acute cases, where a single large dose of iodine has been taken into the organism, provided death does not ensue during the first violent attack of the poisoning.

They are:

1. Nervous disturbances.
2. Derangements of digestion.
3. Affections of the mucous coats of the eye, nose, and throat, with anomalies of secretion.
4. Affections of the skin.
5. Atrophy of certain glandular organs.

The pathogenesis of the digestive derangements and of the impairment of the nutrition of the entire body dependent on them has been already discussed. The nervous derangements which characterize iodism are exceedingly variable in form and intensity. By many authors their occurrence is positively denied. Frequently they are limited to the trifling symptoms of ivresse iodique referred to above. It is evident, however, from the communications of Wallace and Rodet,[1] that they may at times attain dangerous proportions, since those observers have repeatedly observed severe motor and mental disturbances of the character of general paralysis. A very frequent nervous symptom of iodism, according to both Ricord[2] and Wallace, is neuralgic pains in the lower and anterior part of the left epigastrium. Wallace designates this symptom as pleurodynia; Ricord regards it as a neuralgic affection of the fundus ventriculi.

Of the affections of the mucous membranes, the conjunctivitis, which consists in reddening of the conjunctiva and marked increase in the secretion of tears, is often developed, according to Ricord, on the second or third day after the beginning of the iodine treatment. Paul Bernard[3] frequently saw it develop during the second or third month of the treatment.

The affections of the mucous membranes of the nose and throat — the coryza and angina of iodism — are more common. Some authors state that salivation is a rare symptom of iodism, while others have never met with it in this connection. It is said that it can be distinguished with certainty from mercurial salivation by the salty taste, and by the absence of fœtor ex ore, stomatitis and swelling of the glands. That the last symptom is not invariably wanting, is proved by Rose's case, in which the extreme salivation was accompanied by a mumps-like swelling of the glands.

The iodine coryza is characterized by a copious secretion of watery mucus, moderate redness, and slight swelling of the nasal mucous membrane. In the angina the patients complain of intense itching in the throat, and not so much of difficulty in

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[1] Gaz. méd. de Lyon. 1860.
[2] Gaz. méd. de Paris. 1869.
[3] Thèse. Strasburg. 1863.

swallowing; the posterior wall of the pharynx is deeply reddened, and somewhat intumescent. The coryza is, as a rule, combined with a tolerably intense frontal headache.

Sartisson (loc. cit.) has attempted to explain the pathogenesis of the affections of the mucous membranes in iodism. He suggests it as possible that potassium iodide, which is eliminated in the saliva and nasal mucus, may be decomposed by the carbonic acid and the chlorides in these secretions; the iodine which is thus set free could then act as a direct local irritant on the adjacent mucous membranes, and produce the coryza, the conjunctivitis, and the angina. The recent observations of Binz tend to support the theory of the occurrence of such decompositions; but still we cannot at once and unconditionally exclude the other possibility, that the disorders in question may originate in anomalies in the innervation of the blood-vessels and glands of those mucous membranes. The peculiar impairment of sensation in the mucous membranes in bromism is sufficiently analogous to render such a pathogenesis conceivable. Definite knowledge on this point can, however, only be attained by new researches and observations.

The iodine exanthemata are variable in form, and appear in various localities. The form that is most commonly met with is an eruption of acne-like nodules on the skin of the face (forehead, temples), neck, and the upper half of the thorax; more rarely this extends also over the abdomen and extremities.

Bazin[1] assumes three different forms of iodine exanthem. The mildest form is the *erythematous*, which appears in the shape of more or less universal urticaria-like knobs. Out of this form the second, more common *papular* form is developed. The larger papules are surrounded by areolæ, which are often confluent, and present a deep red color, vanishing for a moment on pressure. Finally, a *pustular* exanthema is sometimes developed from the papular form; it occurs in scattered spots on the face, thorax, and extremities. Occasionally a few of the pustules develop into small dermal abscesses. We must, finally, make room here for the statement made by Mercier,[2] that Kuess,

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[1] L'Union méd. 1866.

[2] L'Union méd. 1860.

in Strassburg, has not unfrequently met with œdema of the eyelids, the skin of the abdomen and the forearms, in connection with iodism.

Iodine exanthemata run their course without fever, and, like all the symptoms so far mentioned, vanish spontaneously when the remedy is discontinued.

Before speaking of the atrophy of the mammæ, we must, for the sake of completeness, mention the fact that Kuess is said to have frequently observed hemorrhages from the lungs during the employment of the iodine treatment; while on the other hand, in a few isolated cases, metrorrhagia or habitual increase of the periodic menstrual flow, has been demonstrated.

It is generally admitted that the female breast is the only organ which may undergo complete atrophy as a result of the action of iodine. Hufeland first suggested, over fifty years ago, the possibility that atrophyof the testicles might also be produced by the iodine treatment; his idea found a ready acceptance, and was quoted so often by one author after another, that it gradually and imperceptibly came to be accepted as a fact. It has been pointed out, however, that there is an absolute lack of observations which might serve to prove the influence of iodine in causing atrophy of the testicles. A similar statement cannot be made with regard to its action on the mammæ. Although all authorities, and especially Ricord, agree that it is a very rare occurrence, still cases are constantly occurring from time to time, in which the atrophy of the mammary glands is unquestionably an effect of the iodine treatment. As yet we are entirely unable to understand this fact. It is, however, not more problematical than the analogous action of iodine in goitre, which at the present day is so generally admitted that it no longer causes astonishment.

In the pathologico-anatomical connection, the cases of Rose and Hermann constitute almost the only sources from which we can draw information. The following are the most important points which can be deduced from them.

Rose found free iodine in the stomach and alimentary canal, although originally the tincture had been injected into the cysts; the mucous membrane was colored brown by it. The kidneys

also, on section, presented a brown color, which gradually disappeared on exposure to the air. In the pelves of the kidneys there were slight hemorrhages; the other organs were all normal.

Hermann (internal poisoning by tincture of iodine) found the mucous membrane of the pharynx, epiglottis, and œsophagus covered in spots with an orange-yellow pseudo-membrane; the spots were partly isolated and partly confluent. Beneath the false membranes the mucous coat was swelled and suppurating. In the stomach the coloration produced by the iodine was the only thing that could be discovered.

In the present rudimentary state of our knowledge regarding acute iodine-poisoning, we possess but few special points on which a rational treatment can be based. Starch, and, according to Husemann, egg albumen, which is quite as efficient on account of its affinity (?) for iodine, may be used as antidotes. Aside from them, we must for the present rest contented with the fulfilment of all the symptomatic indications, which need not be here detailed. It is a question whether something might not be accomplished by the use of agents which relax the muscular coat of the arteries, *ex. gr.*, nitrite of amyl.

The phenomena of chronic iodism can, as has already been mentioned, be relieved by suspending the iodine treatment. The disturbances of nutrition, the weakness, loss of flesh, and gastric disorders, which may remain behind, require a careful and appropriate strengthening treatment.

CHAPTER III.

POISONING BY BROMINE AND ITS COMPOUNDS, ESPECIALLY POTASSIUM BROMIDE (BROMISM).

The toxicological importance of the bromine compounds depends principally on the therapeutic employment of potassium bromide, which, in spite of the contradictory statements of clinical authorities as to the value of the agent, is constantly becoming more extended. The poisonousness of elementary bromine and of some of its other compounds (hydrobromic acid,

etc.), which has frequently been demonstrated experimentally, is of but slight importance to the practising physician, so long as those preparations are as little used as at present.

We will, therefore, touch but briefly on poisoning by free bromine ; but both theoretically and practically the interesting poisoning by potassium bromide demands a more searching investigation.

Bromine is at ordinary temperatures a deep reddish-brown, heavy liquid (sp. gr. 2.97). When exposed to the air it gives off dense orange-yellow vapors, which are taken up with tolerable readiness by water, and impart to it the characteristic bromine odor and a yellow color. In its chemical relations it resembles chlorine and iodine.

In the liquid form bromine is one of the most active corrosive poisons ; in the gaseous form, one of the most poisonous, irrespirable gases.

Balard, the discoverer of this element, and Berzelius drew attention to the deleterious action of bromine on animal and vegetable substances, which depends upon the strong affinity of the element for hydrogen, with which it unites to form hydrobromic acid. In this way bromine decomposes the animal tissues, the coloring-matter of the blood and fat, and coagulates solutions of albumen.

Glover[1] found that if solutions of egg albumen were treated with a certain amount of bromine water, a coagulum was formed, but the yellow coloration of the bromine disappeared.

On the skin, liquid bromine produces an intense yellow coloration, blistering, and when its action is prolonged, deep eschars. Analogous effects are produced by the application of bromine to the mucous membranes. The symptoms of the acute gastro-enteritis which rapidly follows the introduction of the poison into the digestive tract are, however, somewhat complicated by the respiratory disturbances which are caused by the penetration into the air-passages of the bromine vapors developed in the body.

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[1] Edinb. Med. and Surg. Journ. No. 152. 1842.

Smaller doses, such as dilute aqueous solutions of the element, cause, as might be expected, less severe derangements; they consist in a burning sensation in the œsophagus, pain in the epigastrium, salivation, nausea, vomiting, diarrhœa, and colicky pains.

Besides these effects, which have been demonstrated by Glover[1] and Barthez,[2] by experiments on animals, and by Hoering, Butzke, Heiemerdinger,[3] and Fournet,[4] by experiments on human subjects, Blake,[5] Glover, and Barthez have also observed the phenomena produced by injecting pure bromine and bromine water into the veins of mammals. When pure bromine was employed, death ensued immediately, with tetanic spasms—evidently in consequence of instantaneous coagulation of the blood. The injection of bromine water also produces at first violent general spasms, which, however, cease in a few minutes, if the concentration of the bromine solution does not exceed a certain limit. In many of the animals experimented on by Glover and Barthez, coryza with violent sneezing and lachrymation was subsequently developed. The respiration and pulse were at first very much accelerated, but became gradually weak and slow; repeated vomiting, and evacuation of the bowels and bladder ensued. After small doses the animals gradually recovered from these symptoms; after larger and fatal doses, the respiration finally became very labored, a bloody froth oozed from the mouth of the animal, violent general tremor set in; the heart's action ceased in from one-half to one and a half hours.

The inhalation of bromine vapors causes the same phenomena as are produced by all irrespirable gases. In the milder grades of the poisoning they are the symptoms of irritation caused by the action of the gas on the sensitive nerves of the mucous membranes, and also reflex symptoms, viz., lachrymation and salivation, spasmodic contraction of the orbicularis palpebrarum, coryza, cough, and moderate oppression; in the severer grades, besides the above-mentioned symptoms, a feeling of suffocation,

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[1] Vid. supra.

[2] Cf. Frank's Magazine. I. p. 386 et seq.

[3] Hasselt-Henkel's Toxikol.

[4] Frank's Magazine, loc. cit.

[5] Edinb. Med. and Surg. Journ. 1847.

great anxiety, burning pain under the sternum, headache, dizziness, and finally, when the bromine vapors have been very concentrated, spasm of the glottis and asphyxia.

Up to this time only a single case of internal poisoning by liquid bromine has been recorded in medical literature. The case was that of a man in New York, who took one ounce of the substance with suicidal intent.[1] The result was of course fatal. Besides this, a case of quite serious external injury by liquid bromine is reported from the manufactory of iodine and bromine at Cherbourg. In consequence of the breaking of a stopcock in a vessel filled with bromine, two persons who were working with it were splashed with the substance as it escaped, and one of them sustained considerable injuries on the hands and forearms. The skin was entirely destroyed wherever it had been touched by the poison, and several months elapsed before the patient recovered from the injury.[2]

No evidence can be adduced from the literature of the subject to prove that the vapor of bromine exerts any serious injurious effects on the workmen who have to deal with that substance. In the text-books, it is true, we read of morbid affections to which the workmen in bromine factories are frequently subjected — of a conjunctivitis and ebrietas e bromio — which Chevallier in particular is said to have described. We have not been able, however, to find anything like such a statement in the only article on the subject that has been published by Chevallier. That article consists principally of the letters of two manufacturers who, in response to Chevallier's inquiries, declare that their workmen suffer from no peculiar disorders. We might perhaps conclude from this, that the workmen are usually but little exposed to the poisonous vapors. In a case reported by Duffield the inhalation of concentrated bromine vapors produced an attack of spasm of the glottis which only yielded to prolonged inhalation of steam. The assumption of Diez[3] that laborers in salt-mines are subject to a sort of necrosis of the

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[1] Reported by *Snell*, New York Med. Record. 1851.

[2] *Chevallier*, Ann. d'hygiène. publ. 1842. 2. p. 313.

[3] In *Husemann*, Toxicol.

lower jaw-bones, due to the action of bromine, has so far not found the confirmation which it greatly needs.

In the treatment of cases of poisoning by bromine we are unable, on account of the scarcity of the observations at our disposal, to recommend anything more than a mere symptomatic treatment.

Both the toxic and therapeutic actions of potassium bromide and of the other neutral bromine compounds, sodium, ammonium and calcium bromides, have of late years been very actively discussed, and the literature of the subject is consequently very abundant.

Before we direct our attention to the details of the symptoms of poisoning, we must first briefly consider the important question whether the alkaline and earthy bromides, as such, have a specific action on the animal organism, or whether the bromine in these salts has no effect, their action being due entirely to the base present.

An affirmative reply to the latter portion of this question has been given by a number of authors who have sought to establish the point principally by experiments on animals, while the specific action of bromine is chiefly supported on the grounds of practical therapeutic experience. However, some clinical authorities also have denied this specific action of bromine. Especially since the poisonous action of the potash salts has become generally known, it has been repeatedly asserted that the therapeutic, as well as the toxic effects of potassium bromide, must be ascribed to the potash which it contains.

It seems to us that these differences of opinion are not by any means irreconcilable, if we take into account the variety of the methods by which the discordant results of the different authors were obtained.

It must in the first place be noted that the so-called bromism, the form of poisoning which occurs after the administration of potassium bromide, and is considered characteristic, has been observed only in human beings, and then only after prolonged use of the agent. It is not at all astonishing that experiments on animals, which are necessarily limited to a disproportionately shorter period of observation, should have afforded noth-

ing analogous. In them, as is evident from the observations of almost all experimenters, only those little characteristic phenomena occur which we are accustomed to see after poisoning by the potash salts. There is an unquestionable similarity between the action of the potash salts in general and of potassium bromide in particular, especially on frogs, and, as far as the general phenomena are concerned, on mammals; but still a closer analysis shows that even in the experiments on animals there is no positive identity in their action. Thus, Steinauer[1] very properly draws attention to the fact that Schouten's[2] investigations on the blood-pressure by no means agree completely in their results with those obtained by similar experiments with other potassium salts. In the experiments on animals, it is true, the action of the potassium may always play the principal part, especially when the salt, as has been done by most experimenters, has been directly introduced into the circulation by injecti n into a vein. The phenomena of bromism, however, as they occur in men after the use of potassium bromide, must unquestionably be ascribed to the specific action of the bromine, if the statement recently made by Starck,[3] should be confirmed. That observer found that the specific symptoms of bromine-poisoning (nervous derangements, exanthem) make their appearance in men after protracted use of sodium bromide also.

The analogous question whether the anti-epileptic and hypnotic actions of potassium bromide are also to be referred to the bromine in the compound, of course cannot be settled here.

Let us pass to the description of the effects of potassium bromide on the animal organism.

Regarding the chemical properties of the drug, it is enough to state that it is a neutral salt, which crystallizes in cubes, is

[1] Virchow's Archiv. LIX. 1874.

[2] Arch. d. Heilkunde. XII. 1871. We do not believe that the question has been settled by *Schouten's* researches. On page 114 we read in leaded type . . . . "that the doses, which are used in therapeutics, in fact increase the frequency of the pulse, but at the same time *diminish the blood-pressure*" (unlike the other potash salts, which increase it). On the other hand, on page 116 he tells us that doses of potassium bromide, which do not endanger life, first cause an increase in the blood-pressure. Which, then, is the usual effect?

[3] Allg. Zeitschr. f. Psychiatrie. 1874.

readily soluble in water, and in its chief characteristics is analogous to the corresponding chlorine compound.

The data concerning its conditions of absorption are given in detail in the work of Clarke and Amory;[1] according to them it is readily taken up by all the mucous membranes. When a moderate quantity dissolved in water is taken on an empty stomach, it is absorbed in about half an hour.[2] The rectum absorbs the agent more slowly, but quite as surely, while it is not taken up at all by the external skin. It is eliminated chiefly through the kidneys. The first traces of bromine, as early as ten minutes after the administration of the dose, are found in the urine. Rabuteau[3] asserts, however, that this excretion normally (without special administration) contains small traces of potassium bromide. The major part is removed from the body in the urine during the first twelve hours, though the elimination still continues after three days have elapsed. The assertion made in many hand-books, that after the administration of potassium bromide free bromine appears in the expired breath, lacks confirmation entirely. The elimination of the substance through the external skin has been demonstrated by Bill[4] and Bowditch.[5] The former found it in the water with which the skin was washed, the latter discovered it in the sweat, produced artificially by a Turkish bath. Rabuteau also, after the internal administration of the salt, found bromine in the saliva and the nasal mucus; Bill found the bromurets (Bromüre) in the secretion of the lungs, in the pharyngeal mucus, and in the fæces.

With regard to what becomes of the salt in the organism, our knowledge is still somewhat incomplete. Clarke's supposition that the free acid of the gastric juice displaces the bromine from

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[1] The physiological and therapeutical action of the bromide of potassium, etc. Boston, 1872.

[2] Since these authors believe that bromide of potassium is decomposed by the acid of the gastric juice and bromine thereby set free, they recommend that the salt should always be administered on an empty stomach (when the gastric secretion is neutral). They evidently forget that the solution of the salt itself may act as an irritant and excite the secretion of true gastric juice.

[3] Gaz. hebdom. 1868.

[4] *Husemann* in Virchow's and Hirsch's Jahresb. 1868 (Amer. Journ. of Med. Sci.).

[5] Ibid. Abstract from Boston Med. Journ. 1868.

it, has not only not been proved by experiment, but as an hypothesis is in the highest degree improbable. We know, that even the iodine of the potassium iodide, a much more unstable compound, is not set free in the stomach. Binz,[1] moreover, has demonstrated that, unlike potassium iodide, the bromide cannot be decomposed by carbonic acid in presence of active oxygen, and he observes further that at a low temperature it is not decomposed even by nitric, nitrous, or hyponitric acid. In consideration of these facts it is hardly conceivable that the small quantity of the free acid in the stomach could exert a more powerful action on the potassium bromide. On the other hand, there is a considerable basis of probability for the assumption that a double decomposition takes place between the common salt, which is present in large quantities in the stomach, and the potassium bromide, as a result of which potassium chloride and sodium bromide are formed. In the urine the bromine appears combined with an alkali as a bromide, and according to the statements of Rabuteau, Bill, and Bowditch, partly also as a bromuret (Bromür).[2] The form which the potassium bromide assumes in the blood and tissues is still unknown. However, the effects of the salt on human subjects, as well as Binz's observations on the behavior of its congener, potassium iodide, renders it probable that the action of the bromine component is felt somewhere in the organism, unless, indeed, we

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[1] Deutsche Klinik. 1873. No. 48, and Virchow's Arch. LXII. 1874.

[2] The terms *Bromür* and *Bromid* of the German refer to the saturating capacity of the element with which it is combined, the lower saturating capacity being indicated by the former termination—"*ür.*" Thus, what was known as protobromide of mercury, corresponding to the chlorine compound generally known as calomel, would be *Quecksilberbromür*, the calomel being *Quecksilberchlorür ;* while the bromine compound corresponding to corrosive-sublimate, perchloride or bichloride of mercury, would be *Quecksilberbromid*, corresponding to *Quecksilberchlorid.* When an element forms only one series of compounds, as potassium, the terms ending in *ür* and *id* are, by some, used indiscriminately. The same remark applies to the iodine compounds *Iodür* and *Iodid*, and to the oxygen compounds *Oxydul* and *Oxyd*, the presence of the *u* in the final syllable indicating the lower saturating capacity of the element. In the present chemical nomenclature a similar terminology is practiced, and we have ferrous and ferric compounds, mercurous and mercuric compounds, as well as nitrous and nitric or sulphurous and sulphuric acids, etc.—TRANSLATOR'S NOTE.

accept the theory of Steinauer (loc. cit.), who assumes that in those bromine compounds, in which the possibility of a separation of the bromine is not given (among which he numbers potassium bromide), the substituted bromine-atom modifies the action of the other constituents (in this case potassium).

The results of physiological researches on animals (frogs, rabbits, cats, dogs, etc.) have, as has been already stated, led the majority of the authors[1] to the conviction that potassium bromide produces entirely the same effects as the other potash salts. These effects consist in their essence in a diminished activity or paralysis of the central nervous system, and paralysis of the heart, while the peripheral nerves and the striated muscular fibres are left unaffected by the poison. To avoid repetition, we refer the reader to the chapter on the potash salts for an account of the experimental data in question.

From the study of the experimental works on potassium bromide, no other conclusion can be drawn than that the results obtained required to be identified with those of potassium-poisoning, if we put out of the question the as yet unexplained discrepancies which are contained in the work of Schouten. The facts adduced do not appear to us to warrant any further conclusions. The assumption of a disorder of nutrition and a diminution of the nutritive changes produced by potassium bromide, which emanated from Schouten, is evidently no more than an hypothesis. The behavior of the arterial vessels plays an important rôle in the experiments hitherto published. The majority of the authors[2] assume, on the basis of numerous observations of the retina of the eye, the vessels of the pia mater, the arteries of the mesentery, the ears of rabbits, and the web of frogs, that potassium bromide produces a contraction of the muscular coat of the vessels, and some few believe that the entire action of the poison on the nervous system can be explained in this way. Considering the great unreliability of all

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[1] *Eulenberg* and *Guttmann*, Med. Centralbl. 1867.—*Lewizky*, Virch. Arch.—*Damourette* and *Pelvet*, Bull. gén. de thérap. 1867.—*Schouten*, loc. cit., etc.

[2] *Lewizky*, *Saib-Mehmed*, *Clarke* and *Amory*, *Saison*, *Witchead*, and *Damourette* and *Pelvet.* Others have either seen an immediate dilatation of the vessels (*Nicol* and *Mossop*, by observation of the retina), or dilatation following contraction.

the methods of investigation hitherto employed, even without taking into account the dissenting statements made by other authors, we cannot attach much weight to the above observations. For the rest, even if its influence in causing contraction of the vessels could be positively proved, we should hardly attain thereby to a better understanding of the mode of action of potassium bromide.

It is evident that these experimental results cannot explain the essence of those phenomena which result from a prolonged impregnation of the human organism with potassium bromide. They do not even allow us to conclude that the phenomena of bromism are produced by the potassium, so long as no one has demonstrated that for the production of this complex of symptoms the prolonged administration of any other potash salt is sufficient. Very little consideration is necessary to show that the results of an experiment on an animal, which, apart from the different method of application, only extends over a few hours, cannot be compared with the state of affairs which results from feeding the human organism with the poison for weeks, often for months, and even for years. We must therefore, in discussing bromism, entirely disregard these experimental results. The fact that manifestations of an affection of the central nervous system—namely, depression of the functions of the brain and spinal cord—have been observed both in the chronic poisoning by potassium bromide in men and in the experiments on animals, indicates that the above-mentioned organs are the chief points of attack for the action of the poison, not only in chronic and acute bromide-poisoning, but also in poisoning by the potassium salts.

Bromism, or the form of intoxication produced in men by potassium bromide, arises, as has been already frequently stated, exclusively from the therapeutic use of this drug in various nervous diseases. It is usually the result of a prolonged treatment, in which the remedy has been used in doses of from one to twenty grammes (from fifteen grains to five drachms) per diem for months or even years.

In rare cases, however, bromism assumes the character of an acute poisoning, namely, when, as is so often the case in the

beginning of treatment with the preparations of iodine, the symptoms of poisoning present themselves after the administration of only a few moderate doses.

Thus, Johnson[1] observed in several of his female patients, after the administration of the first small doses of potassium bromide, general tremor of the muscles, formication, and paretic phenomena, which lasted only a short time. Bowditch also (loc. cit.) saw, in a few cases, restlessness and nervous agitation follow the use of this substance. Laborde[2] made experiments on himself to ascertain the action of single large doses (15 grammes =half an ounce). They caused at first a salty taste in the mouth, increased secretion of saliva, frequent eructations, and nausea. In an hour and a half nervous disturbance set in, which lasted for eighteen hours. Almost all of the functions of the central nervous system were to some extent affected. Depression of spirits, dizziness, disturbances of vision, somnolence, and sleep with bad dreams, indicated a decided affection of the brain. The power of voluntary movements was greatly diminished, the gait was unsteady, and the tongue thick. Finally, he experienced also a decided blunting of sensibility and of reflex excitability.

The power to resist the action of the drug varies very much in different individuals. Voisin[3] remarks that children bear exceedingly large doses (12 grammes [three drachms] per diem) without injury. In adults, of whom women are said to be in general more readily affected than men, the rapidity with which the phenomena of poisoning appear depends on the size of the daily dose of the bromide. Small doses of from 1 to 3 grammes (from fifteen to forty-five grains) per diem can be administered for months without injury. That this rule, however, is not without exception, is shown by Cholmely's[4] case, in which, although only from 1.8 to 2.7 grammes (from twenty-eight to forty-one grains) were given per diem, the bromine-rash made its appear-

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[1] *Husemann* in Jahrsber. of Virchow and Hirsch. 1868.

[2] Gaz. méd. de Paris. 1869.

[3] Arch. gén. de méd. XXI. 1873.

[4] Bost. Med. Journ. 1869.

ance. On the average, according to Starck,[1] the symptoms of poisoning appear in the second or third week after the beginning of the treatment. Voisin[2] expresses himself much less decidedly on this point. He states that bromism occurs in individuals who have been taking the drug daily in doses of from 4 to 10 grammes (from one to two and a half drachms) for several months or years, and that we are unable to explain why the symptoms show themselves earlier in one case and later in another.

It is certainly not an unimportant point that the most of the individuals on whom bromism has hitherto been studied were not in a normal condition, but were, on the contrary, epileptics, whose entire systems, even before the beginning of the treatment, were in a state of profound disturbance. Starck mentions particularly that he has seen the more serious forms of bromism almost exclusively in epileptics in whom the disease had existed for many years, and was associated with advanced psychical deterioration.

The symptoms of bromism are composed of:

1. Disorders in the sphere of the central nervous system.
2. Anomalies of digestion and nutrition.
3. Affections of the skin.

With reference to the pathogenesis of the clinical picture, in which sometimes one set of symptoms and sometimes another predominates, but little can be said.

We might include the entire intoxication in the sphere of the so-called cumulative actions, but we are unable to determine whether it is necessary for the production of this toxic effect that a certain amount of the injurious agent should have accumulated and been retained in the organism. Voisin, at least, is of the opinion that the occurrence of bromism is connected with disorders in the action of the skin and the elimination of the poison from the body. At all events, it is a striking point that

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[1] Loc. cit. p. 72. The amount of bromine administered previous to the development of the bromism varied, for men, between 100 and 140 grammes (three and four and a half ounces); for women, between 40 and 110 grammes (one and one quarter and three and a half ounces).

[2] Loc. cit. p. 51.

the resistance of the organism ordinarily ceases abruptly after the patient has taken the poison for a long time without detriment.

The disorders of digestion and nutrition, which are generally developed gradually, are less difficult to explain. The cutaneous affection is connected by many authors with the elimination of the bromine through the glands of the skin, although absolute proof of its production in this way cannot be adduced.

The phenomena do not follow any exact law in regard to the order in which they appear. Usually the nervous disturbances precede the development of the exanthem. With regard to the course, Voisin distinguishes an acute and a lingering, slow form; he also recognizes a bromine cachexia, which is characterized by a general decline of the nutrition.

The detailed description of the symptoms presents some difficulties, since, in the observations reported by the writers on the subject, the majority of the patients were weak-minded; and it is frequently impossible to determine exactly what symptoms are to be attributed to the primary disease, and what to the toxic action itself.

As a rule, the symptoms of bromism develop with tolerable rapidity in the course of a few days, and without any preliminary prodromal stage. They begin with subjective feelings of great exhaustion, weakness of the muscles, and vague pains through the whole body. The patients become depressed in spirits, listless, forgetful and apathetic, and have a reeling, extremely unsteady gait, and a thick, indistinct mode of speaking, associated sometimes even with partial amnesia. Single words fail them in conversation. Voisin cites an interesting case of a patient who manifested this striking disturbance of the memory also in writing: he wrote some words which were quite incomprehensible and other words only half-finished, in bewildering succession (agraphia).

In higher degrees of bromism, absolute stupor supervenes with marked diminution of mobility. The patients then very frequently, at every attempt to move forward, fall down; in other cases, still, the movements are ataxic, or attempts at movement provoke a general and prolonged trembling of the

muscles. Voisin found that the sensitiveness of the skin was unchanged; consciousness also is never completely lost. The entire condition has by many authors been compared with the later stages of the general progressive paralysis of the insane.

Voisin also asserts that there is another form of bromism which is characterized by paroxysms of insanity and delirium. Starck, on the other hand, believes that these symptoms, which are observed in epileptic patients, are not to be considered as due to the action of the potassium bromide, but must be explained by the checking of the epileptic fits.

One of the most striking and most characteristic symptoms of bromism consists in the peculiar change in the reflex excitability of the palate and throat—a change, however, in which the sensibility of these parts does not participate. The reflex excitability of this circumscribed region is so completely suspended that even the roughest touch does not provoke the ordinarily active reflex contractions of the pharyngeal muscles. This remarkable fact, which we are still unable to explain, has been made use of recently in laryngoscopy. Bill observed, even after small doses of potassium bromide, a marked diminution in the sensitiveness of the mucous membrane of the urinary tract, and of the conjunctiva; Gatumeau saw complete anæsthesia of the conjunctiva.

In regard to the changes which take place in other parts of the body during bromism, these consist in more or less marked disturbances in the vegetative sphere: the patient has a bad appearance; his face is of an earthy hue; the expression is dull, and the mobility of the countenance is impaired; the mucous membranes appear pale; the excretion of saliva is sometimes increased, but more frequently the cavity of the mouth is dry, the breath ill-smelling, and the nose stopped by hardened secretion; the weight of the body soon diminishes in consequence of a loss of appetite, and also sometimes as a result of an obstinate diarrhœa. In a few patients Voisin observed dyspnœa and an irritating croupy cough.

The organs of circulation suffer during bromism from no especially characteristic derangements; sometimes palpitations

are observed, and sometimes weakness and irregularity of the pulse, or decided retardation of the same.

The temperature of the body is not sensibly affected. So far as the soporific action of potassium bromide and its effects on the sexual instinct are concerned, it seems to us that a discussion of these points is superfluous, since the above-mentioned effects are chiefly observed after small non-poisonous doses.

The exanthemata, which belong among the most constant symptoms of bromism, arise at times independently of the above described neuropathic symptoms, at others in conjunction with them. They manifest themselves during the first two to four weeks after the commencement of the bromine treatment, last, as a rule, about a week, and then disappear independently of the fact whether the bromine treatment is maintained or interrupted. They occur, according to the united testimony of authors on the subject, in 60 per cent. of all cases where the bromine treatment is carried out (in men more frequently than in women). Starck, moreover, declares that the affections of the skin ordinarily occur sooner in the female sex (after from fourteen to twenty-one days) than in the male (from thirty-three to forty-six days).

The exanthem, as a rule, assumes one of the forms of acne, and consists of discrete (never confluent), dark reddish blotches, which attain the size of small-pox pustules, and like them, at a later stage, show a depression in the centre, and suppurate. They heal, leaving a dark-colored spot on the skin.

Neumann,[1] who examined the affection very closely, found inflammation of the glands of the skin with swelling of the cells of the cutis vera, and increase in size of the papillæ. The exanthem is usually confined to the face, and especially to the region of the brow, mouth, and nose ; it appears less frequently on the cheek, neck, breast, and back. The affection is neither painful nor combined with itching, and runs its course without fever.

In rare cases the skin disease occurs in the form of erythema, urticaria, eczema, ecthyma or furunculous formations, as appears from the observations of Voisin and Wood ;[2] Turnbull

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[1] Wien. med. Wochenschr. 1874.

[2] Brit. Med. Journ. 1871.

and Witchead[1] noticed similar phenomena, and Neumann observed in an adult, who had been taking potassium bromide for a period of nine months, furuncles on that portion of the face which is covered with hair.

The course and termination of bromism depend particularly upon whether or not the administration of the poison is discontinued at once upon the occurrence of toxic effects. If the drug be discontinued at the right time, *i. e.*, as soon as possible, the phenomena under consideration usually cease with tolerable rapidity and without permanent injury to the patient; at most there will remain indefinite, unpleasant sensations, wandering pains, and general debility, which now and then persist for some time. Instances, however, are on record where treatment with bromine has produced fatal results. Such cases have been described by Hameau[2] and Falret.[3] Death ensued suddenly with phenomena of asphyxia, apparently from paralysis of the heart or of the nerve-centres.

It is not our province, as we believe, to discuss the unfavorable effects upon the course of the disease, and even upon the patient's life, which sometimes follow a suspension of the bromine treatment in cases of epilepsy. Still, the remark may here be made that Starck, who is occupied with comparative experiments on the action of sodium bromide and potassium chloride, has up to this time observed a single case where, after the use of five grammes (four scruples) of sodium bromide per day for three weeks, bromism developed in the most unmistakable manner, with the skin affection, etc.

In most cases it suffices, in treating bromism, to intermit the use of the drug at once on the development of toxic symptoms, whereupon they cease of themselves; at the same time it is well to supplement this treatment by a strengthening diet, frequent warm baths, and other diaphoretic procedures, as suggested by Voisin.

Specific antidotes and other means of combating bromism are not known.

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[1] Quoted by *Starck*, loc. cit.

[2] Journ. de Bord. 1868.

[3] Quoted by *Starck*, loc. cit.

SECOND DIVISION.

Poisoning by Acids.

A. *Mineral Acids.*

CHAPTER I.

POISONING BY SULPHURIC ACID (SULPHOXYSM).

Sulphuric acid (acidum sulphuricum, SO_3) is well known as one of the most powerful acids, and is noted for its strong affinity for water. When the concentrated acid is mixed with water, the commingling of the two is accompanied by an extraordinary rise in temperature. Sulphuric acid is odorless, gives off no fumes at ordinary temperatures, and, even when highly diluted, tastes exceedingly acid. Since it finds various applications in technology and trade, and is ordered in various preparations as a medicine, it may also cause poisoning in various forms. The ordinary oil of vitriol (English, or Nordhäusen,[1] sulphuric acid, acidum sulphuricum crudum), as well as diluted sulphuric acid, —frequently called "oleum" in common parlance, and diluted with water in the proportion of 1:5,—indigo sulphate solution, Haller's acid (Elixir. acid. Halleri), etc., are therefore the preparations which come under the cognizance of toxicologists.

The nature of this poison is such that the greatest importance attaches to the effects of its immediate contact with the parts, while the more remote effects which follow its absorption into the blood, as in the case of other poisons, remain in the background, and but seldom come under observation. The chief characteristic, therefore, of sulphuric acid poisoning, is its local

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[1] The *ordinary* oil of vitriol (H_2SO_4) is generally known on the continent as "English sulphuric acid." The Nordhäusen acid is called by chemists "fuming sulphuric acid," and consists of $H_2SO_4.SO_3$ ($=H_2S_2O_7$)—old system $HO.2\ SO_3$. The two are not identical, as would seem to be here implied.—TRANSLATOR'S NOTE.

action, and it is only recently that absolute proofs have been adduced, which show that the acid can find its way into the blood by absorption, and there produce still other results.

What happens, then, in the first place, when sulphuric acid comes in contact with organic tissues, and particularly with those belonging to the human body? The acid satisfies its affinity for water by withdrawing it from the tissues, and the activity with which this takes place is in direct proportion to the degree of concentration of the acid. Simultaneously the tissues, under its influence, become profoundly disorganized; for the acid not only takes up the bases contained in them and which are combined with weaker acids, but also dissolves everything that it comes in contact with, thus destroying the continuity of the tissue. Not one of the tissues belonging to the living organism has power to offer resistance to the action of sulphuric acid.

Falck and Victor[1] have made very accurate researches with respect to the action of sulphuric acid on various tissues.

In solutions of albumen, sulphuric acid of any degree of concentration above a specific gravity of 1.250 causes precipitates, which dissolve completely in an excess of the acid. Less concentrated dilutions of the acid precipitate albumen but slowly. In defibrinated blood also the acid throws down a precipitate, which is soluble in an excess of the reagent, the blood being at the same time blackened. Fibrin suspended in water dissolves in an acid which has a specific gravity of 1.470, the solution assuming a yellowish-brown color; in less concentrated dilutions it remains unaltered. Muscular tissue is most readily dissolved by sulphuric acid of specific gravity 1.574 to 1.789, the solution assuming a blackish-red color, and the muscle first swelling up into a jelly-like mass. Dilutions of the acid having a lower specific gravity than 1.574 do not dissolve muscular tissue completely, but only dissolve the areolar tissue within it; the entire mass is first turned to a whitish hue, and then converted into a pap which is more or less thick.

The coats of the hog's stomach are completely dissolved within less than twenty-four hours in acid of specific gravity 1.470, the resulting slimy mass being of a blackish-brown color. In acids of a higher or lower degree of concentration, solution takes place more slowly, or even, in very weak dilutions, not at all.

The chemical products of decomposition which result from the action of sulphuric acid on the tissues are not accurately known. According to Mulder,[2] in the tissue decomposed by the

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[1] Deutsche Klinik. 1864. Nos. 1–32.

[2] Cf. *Buchheim*, Arzneimittellehre. II. Aufl. 1859. p. 180.

acid only ammonic sulphate and humic acid, together with free sulphuric acid, can be found.

The question as to the form in which sulphuric acid is taken into the blood, after introduction into the stomachs of men or animals, has not yet been definitely determined.

The possibility of the existence of free sulphuric acid, as such, in the blood of a living man, has already been disproved definitely by Pereira and Buchheim.[1] The acid reaction of the blood, observed by other authors (Walker,[2] Hoelder,[3] Casper[4]) in human victims of sulphoxysm, is considered by Mannkopf[5] as a post-mortem condition, for he himself proved the normal alkaline reaction of the blood in cases of living men who had been poisoned by sulphuric acid. But inasmuch as recently, in many cases of sulphuric acid poisoning, the increased elimination of sulphates in the urine has been demonstrated with absolute certainty, which implies incontestably an actual absorption of sulphuric acid, nothing remains but to assume either a saturation of the acid immediately after its absorption into the blood, or its absorption in the form of sulphates which have already been formed in the stomach or the tissues (Mannkopf [loc. cit.] and others). Improbable as it may appear, *à priori*, that the acid absorbed is neutralized in the blood, further researches are necessary to decide this point in one way or the other.

As regards the elimination from the organism of the sulphuric acid absorbed, it may be considered as settled that the acid leaves the body in the form of sulphates (Schultzen,[6] Mannkopf [loc. cit.]),[7] which appear in the urine in large quantities, chiefly as lime salts. Although this fact has in general terms been long since established (Orfila), it is only recently that it has

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[1] *J. Pereira's* Handbuch der Heilmitellehre, nach dem Standpunkte der deutschen Medicin bearbeitet von *R. Buchheim.* Leipzig, 1846. I. Bd. S. 449.

[2] Monthly Journ. Vol. X.

[3] Würtemburg Med. Corresp.-Blatt. 1852.

[4] Handbuch der gerichtl. Medicin. 5 Aufl. II.

[5] Beitrag zur Lehre von der Schwefelsäurevergiftung. Wiener med. Wochenschr. 1862 and 1863.

[6] Arch. f. Anat. u. Physiol. 1864.

[7] According to *Husemann* (loc. cit., p. 731), Letheby and Miguèl have also proved, by examinations of the urine, the elimination of sulphuric acid through the kidneys.

received the attention which it deserves. It has been found that this elimination in the urine does not continue for a long time; that in the beginning of a case of poisoning this elimination of the sulphates falls from a maximum to zero in a very short time; one has, therefore, no right to infer, from the absence of sulphuric acid in the urine in an acute case, that a state of poisoning by sulphuric acid does not in that particular case exist.

The urine in sulphoxysm is, as a rule, acid; but whether it is so from the presence of other free acids, which have been deprived of their bases by the sulphuric acid, remains yet to be proved. Since such acids, according to this theory, must have formed already in the blood, the alkaline reaction of this fluid is at least not in accord with such an assumption.

Recent observations have shed some light upon the changes which the sulphates circulating in the blood provoke in the organs of the body (Munk and Leyden, Mannkopf). The kidneys, as it appears, are specially affected; they are thrown into an actual state of inflammation, which manifests itself during life by albuminuria and the presence of fibrinous cylinders in the urine, and, after death, by corresponding post-mortem appearances.

Mannkopf holds that a direct irritation of the parenchyma of the kidneys by the sulphates is probable, and remarks that even Glauber's salts, when their laxative effects are prevented by the use of astringents, exert an irritating effect upon the kidneys, causing diuresis, and—in the case of already existing nephritis—aggravating the symptoms. At the same time, however, and quite properly, he declares that these questions cannot be definitely settled until further experiments shall have been carried out.

Cases of poisoning by sulphuric acid belong to the more frequent forms of poisoning which are met with by the practising physician. The reasons for this lie in the accessibility of the poison, and in the widespread, though very superficial knowledge of the effects which it is sure to produce. At the same time, cases of this form of poisoning do not appear to occur with equal frequency in all countries and localities; at all events, certain places, among which is Berlin, furnish a disproportionately large quota.

In the larger number of cases sulphuric acid is used for sui-

cidal purposes, and this occurs very often among individuals of the lower classes, as, for instance, domestics, mechanics, etc. Next come, in the order of their frequency, the cases of accidental poisoning by this substance. These are mostly caused by mistaking the acid for some beverage, an accident which has happened to sober persons, and also to those who were drunk. In a few cases, strange to relate, sulphuric acid has, by mistake, been used in clysters in the place of oil, the error leading to fatal results, as might be supposed.

Sulphuric acid can only be administered with murderous intent to children, and those overcome by heavy sleep or drunkenness. In the case of children, as the literature of the subject informs us, this has occurred often enough; but only isolated cases are known where the acid has been administered with murderous intent to adults while asleep or overcome by the effects of alcohol.

Christison [1] relates that, in the large English manufacturing towns, the crime of throwing sulphuric acid upon a person's face, with the intent of causing mutilation, was not long ago so common that it was declared by parliament to be a capital offence; and von Hasselt [2] states that attempts at murder have been made by pouring the acid into the ear of the sleeping victim.

It is difficult to give exact statistics in regard to the frequency of sulphuric acid poisoning. Of 930 cases of poisoning observed in England, France, and Denmark, 190 were caused by sulphuric acid.[3] Of 527 fatal cases of poisoning which occurred in England during the years 1837 and 1838, only 32 were caused by sulphuric acid. In the Vienna General Hospital the cases of sulphuric acid poisoning constituted nearly one-half (13 out of 30) of all the cases of poisoning which were observed in that institution in the years 1856 to 1858. According to Casper, nine-tenths of all cases of poisoning in Berlin are caused by taking sulphuric acid. Flandin found, among 180 cases of poisoning that occurred between the years 1841 and 1844, only 11 cases of sulphuric acid poisoning, from which it seems that this form of poisoning occurs more rarely in France than in other countries. Moreover, from the figures quoted, which are taken from Husemann's Toxicology,[4] no general conclusion can be drawn other than that sulphuric acid is to be reckoned among the poisons which are very frequently used.

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[1] Loc. cit. p. 160 [German edition].
[2] L. c. p. 166.
[3] Cf. *von Hasselt*, loc. cit.
[4] L. c. pp. 353 and 759.

We ourselves have collected, from the literature of the last fifty years, accounts of 113 well-authenticated cases of sulphoxysm. Of these 37, or 32.7 per cent., were men; 55, or 47.7 per cent., were women; and 21, or 19.6 per cent., children under ten years. Of these, 77, or 68.2 per cent., resulted fatally, while 36, or 31.8 per cent., resulted in recovery. From these figures, it appears that there is a marked predominance of cases among females, a point to which other authors have already called attention. The causes we could only ascertain with certainty in 53 cases: of these 24 were accidental, 16 suicidal, and 13 were cases of murder (children).

As regards the amount of the poison which is requisite for poisoning with a fatal result (dosis letalis), in our opinion no figures can be given which will hold good for all cases. In deciding this point we must have reference solely to the results of practical experience, since the experiments on animals, in other respects so valuable, in this particular case can justify no conclusions with regard to mankind. But in this connection nothing certain can be inferred from the records of cases of sulphoxysm. It very rarely happens that the amount of the poison used can be accurately estimated, and frequently one is also in the dark as to the degree of concentration of the preparation used. Besides, cases have been seen to end fatally, in which it was known that small amounts of the poison had been taken; and others have recovered where it was ascertained beyond a doubt that large amounts of concentrated acid had been taken. Much depends, as will be readily understood, on the amount of solids and fluids contained in the stomach. It makes a great difference also, as regards the course of the illness, whether the case comes under medical treatment early or late. Finally, not a little depends on the part of the body to which the poison was applied; those cases, for instance, where the poison was injected into the rectum, quickly ended in death.

In general, it may be laid down as a rule that any appreciable amount of concentrated acid can produce death; at the same time, external circumstances have an important bearing on the issue, and we do not believe that any more precise rule can be formulated.

The general character of the symptoms which should occur after poisoning by sulphuric acid may be at least inferred, *à priori*, from what has been said above. Still, it would be an

error to expect that all these symptoms would show themselves in every case. Individual idiosyncrasies, and, still more, chance assert their sway here; and though the general features of the disease are in the main the same, yet a closer study of the literature shows that the individual symptoms may vary greatly in character and intensity. These symptoms are not merely the immediate consequences of the local alteration of the tissues; they are due in large part to the reaction of the entire nervous system from the violent irritation communicated to it by the sensory nerves in those portions of the body which have been subjected to the action of the acid. Then, besides, we must take into account the general phenomena caused by the absorption of the poison. Finally, we encounter numerous modifications of the usual complex of symptoms, as soon as the sulphoxysm passes from the acute into the chronic stage. As in these cases, however, there can no longer be any question of a continued action of the poison, but rather of the consequences of the first momentary action, one might very properly think it advisable to discuss these cases in another department of pathology. Nevertheless, there are practical considerations which will not allow us to pass the subject over in silence, especially since, if we were to do so, the practitioner might in some cases be left in doubt in regard to the diagnosis and proper mode of treatment.

The first scene in a case of sulphuric acid poisoning will vary according to whether the poison has been taken for a suicidal purpose, or has come into the patient's hands by an unlucky accident. In the former case, as a rule, the individual will naturally have swallowed a large amount of the poison, while in the latter case the quite unexpected pains and reflex actions which occur at the moment when the acid comes in contact with the parts, will usually cause a sudden expulsion of the poison. It is only in cases where a person, while intoxicated, has mistaken sulphuric acid for some beverage, and, while laboring under this belief, has taken the fluid down as it were at a single gulp, that large amounts of the poison have found their way into the stomach. On the other hand, accidental poisoning involves more risk of the poison entering or coming in contact with the air-passages.

The severity of the affection of the cavity of the mouth will therefore vary in accordance with the manner in which the poison has been taken. The contact of the acid with the mucous lining of the mouth causes a violent and sudden sensation of pain, which varies in severity according to the concentration of the acid, and is designated by the patient sometimes simply as a burning sensation, sometimes as a powerful drawing together of all the parts, combined with an acid taste. If no acid has been swallowed, the subjective phenomena mentioned are limited to the organs of the cavities of the mouth and throat, which almost immediately after the action of the acid show a whitish appearance.[1] If the acid, however, has been swallowed, whether in small or in considerable amounts, the burning pains extend from the mouth to the stomach, and often spread from these rapidly throughout the whole abdomen. In the course of a very few minutes vomiting and violent retching ensue, black bloody masses being sometimes thrown up in large quantities. Frequently at this stage the patients suddenly fall down senseless, and especially delicate individuals (women) are very apt to be seized with trismus and general tetanic convulsions, which are to be considered as reflex phenomena produced by the violent pain.

Death may occur at this stage—that is, a few minutes after the poisoning has taken place; it is then brought about either by the powerful action of the poison upon the system, or by asphyxia due to a direct lesion of the air-passages by the acid. If very concentrated acid has been taken into an empty stomach, the immediate perforation of the stomach and the escape of the poison into the cavity of the peritoneum may be followed by death more or less speedily.

As a rule, however, the affection pursues a less rapid course. Other phenomena are likely to appear before death relieves the patient of the inexpressible torture in which he has been during a period of several hours. The intensity of the local pains increases; there is also a distressing difficulty in swallowing; and, with a raging thirst, the patient is yet unable to get down a

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[1] "As if sprinkled with salep powder" (Taylor).

single drop. Every attempt at swallowing brings on a fresh attack of vomiting and retching. In some cases there is continuous vomiting. At the same time, complete aphonia is often present, and there is almost always copious salivation. The external appearance of the patient is that of a person in a severe and general collapse. The eyeballs are sunk deep in their sockets, the eyes have a staring expression, and the pupils are dilated. The pale skin has a death-like coldness, and is covered with a cold, clammy sweat, while the skin of the face appears much reddened and greatly bloated. The thread-like pulse is frequent, and, as a rule, can be felt only with difficulty; the respiration, according as the air-passages are more or less directly involved, is more or less labored. The alvine and renal secretions are, as a rule, suppressed; only occasionally has diarrhœa been observed, with or without blood, or a spontaneous discharge of urine containing blood or albumen. So far as the operations of the mind are concerned, most patients manifest great depression of spirits, and in all their replies to inquiries, the most profound anxiety is observable. Others will be found, either at times or constantly, in a state of unconsciousness or stupor.

In many cases of sulphuric acid poisoning, death ensues in the course of the first twenty-four to thirty-six hours, often after shreds of mucous membrane, which have become detached through the corrosive action of the acid, have been expelled by vomiting or per anum. These fatal cases, however, differ very much in their external manifestations. Either the unconsciousness passes gradually into coma, and death ends the rapidly increasing collapse, or severe tetanic convulsions precede the fatal issue, as in death by suffocation. In the former case, we are very likely to find afterwards that the stomach was perforated, in which event the vomiting ordinarily ceases altogether some time before death; but in many cases we find ourselves unable to assign any other immediate cause for death, except the exhaustion of the individual's strength from the effects of the powerful strain upon the entire organism. Where the mode of death resembles that from asphyxia, with violent convulsions, we may, as a rule, attribute this result to local changes that have taken place with greater or less rapidity at the entrance of the

air-passages (for instance, œdema of the glottis), in consequence of some of the acid having found its way to these parts.

If the patient, during the time specified, does not succumb to the action of the poison, phenomena of reaction, both local and general, soon appear; the pulse, which was weak before, becomes stronger, the temperature rises, and all the usual symptoms of an inflammatory fever manifest themselves.

At those spots where the poison exerts its caustic action, the parts become red and swollen (from serous infiltration), purulent inflammation gradually sets in, and ulcers develop. These processes become new sources of torturing pain to the patient. In the cavity of the mouth there is often an enormous swelling of the entire mucous membrane, especially of the tongue, in consequence of which it is almost impossible to introduce food into the stomach; and if the posterior portions of the pharynx are involved, there will also probably be more or less dyspnœa. The difficulty in swallowing of course continues; and when, as Mannkopf (loc. cit.) remarks, the eschar first separates from the walls of the mouth and throat, leaving behind a raw surface deprived of its protecting epithelial layer and highly sensitive, this difficulty is greatly enhanced. Salivation also continues, and the saliva flows constantly from the mouth of the patient. The region of the larynx is extremely sensitive to external pressure, an indication that inflammatory changes are also going on in its interior. Throughout the whole length of the œsophagus violent pains are felt, and retching and vomiting are the only response to the patient's attempts to swallow anything. The abdomen, which is usually in a state of distention, is very sensitive to pressure, and the excretions from the bowels and kidneys are, as a rule, still suppressed. Only in rare cases has diarrhœa with dysenteric stools been observed. In the urine, passed naturally or by artificial aid, very large amounts of albumen and casts have recently been detected (Wyss, Mannkopf, Munk and Leyden, and others). Still, albuminuria has not as yet been recognized by all observers as a constant symptom of acute sulphuric acid poisoning.[1]

[1] *Smoler* found albuminuria but once in fourteen cases. Wiener Medicin. Halle, 1861.

Of course, even in this reactive stage of sulphoxysm, the duration of which cannot be exactly defined, the life of the patient is still in great danger, and, in fact, death frequently ensues in the course of the first week after the poisoning, though cases have often been known where,—especially when the action of the poison has been less energetic,—after this lapse of time, the patient was already far on the way towards recovery.

In most cases recovery takes place slowly. It is indicated by a gradual decrease in severity of all the symptoms. The difficulty in swallowing, the pains, and also the vomiting, often last, however, for weeks. Fragments of mortified tissue, having an exceedingly foul odor, are repeatedly voided, either with the stools or with the matters vomited. A number of cases are on record where, after the lapse of several weeks, long tubes of detached (necrosed) mucous membrane were thus removed from the organism; in two cases (Wyss,[1] Trier[2]), for instance, the entire mucous lining of the œsophagus came away in this manner. At this stage one often observes a symptom which closely resembles the globus hystericus: in attempting to swallow, the patient experiences a feeling as if a ball rose and fell in the throat. Recently, Mannkopf has further observed, in several cases of poisoning, neuralgic affections of the intercostal and abdominal nerves; also, in isolated cases, extended and severe hyperæsthesia over the whole trunk, symptoms regarding whose pathogenesis we are as yet entirely in the dark. In the different cases they developed at different times, between the eighth and the twenty-second day after the poisoning.

In this stage, also, the cicatrization of the parts destroyed by the corrosive action of the acid takes place, a process which, in the case of the mouth and pharynx, we can readily observe throughout its entire course. It is this process, too, which after the lapse of months brings the patient, who has successfully passed through all the other stages of the poisoning, face to face with death from starvation. In all such cases we have to deal with cicatricial strictures, which may be located in different portions of the alimentary canal. They form mostly at the inferior

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[1] Arch. d. Heilkunde. 1869.

[2] Schmidt's Jahrb. 1852.

portions of the œsophagus, less frequently in the superior portions; they also form in the cardiac, but especially in the pyloric region of the stomach. In the latter case, proliferation of the tissues has been sometimes observed simultaneously with the stricture, and some authorities even report the development of a scirrhous growth from this proliferating portion. If the stricture has its seat in the œsophagus, or at the cardia, the food taken will, as a rule, be regurgitated before it can reach the stomach. If the contraction, however, is at the pylorus, the food which has been received into the stomach will be vomited up, either at once or after some time has elapsed.

The natural consequence of such alterations of the tissues in the organs of digestion is a slowly progressing inanition, from the effects of which the patient, emaciated to a mere skeleton, ultimately dies.

It is worthy of note that these strictures sometimes first develop after the patient already regards himself as entirely cured, and even after he has been able for a considerable period to take food without any difficulty. The tardy development of a stricture in such cases is due to the presence of an ulcer which cicatrizes but slowly.

As a matter of course, in a treatise like this, all the phenomena which have been observed in the numerous interesting cases of sulphuric acid poisoning recorded in literature cannot be described in detail. Fistulous communications of all conceivable kinds can form between different organs; and, among other things, suppurative parotitis, and paralysis of the sphincter ani, with incontinentia alvi, have been observed

As regards the external appearance of the corpses of persons who have succumbed to acute sulphoxysm, they present but little that is characteristic. The observation has been made that they resist decomposition for an extraordinary length of time, which Casper is inclined to refer to the neutralization of the ammonia formed by decomposition. At the present time we possess no facts which would corroborate this hypothesis, or which would justify us in bringing forward any other. On the external skin, wherever the acid comes in contact with it, changes will be found which extend to a greater or less depth, according to the

degree of concentration of the acid. According to the statements of different authors, it is a very common occurrence to find ribbon-like streaks extending from the corners of the mouth a variable distance downward or outward, on the line of which the epidermis shows a dirty yellowish coloration and a parchment-like consistence. Besides this, one often observes, at various places on the external skin, brownish or rust-colored spots, covered with crusts, beneath which a reddened and often ecchymosed tissue is found. These different changes, of course, represent various grades and stages of local corrosive action.

The lips are usually altered in a similar manner, though often they are quite intact. In the cavity of the mouth the changes observed will be the same as those which are seen during life, *i. e.*, a yellowish-white coloration of the epithelium, which may be lifted off in large patches, and beneath which the tissue appears, at times, only reddened, at others of a dirty color, and at others still mortified or infiltrated with pus. Ulcers are met with in all stages, up to complete cicatrization, in the cavity of the mouth, upon the walls of the pharynx, upon the epiglottis, and in the interior of the larynx. An analogous state of things will be found in the œsophagus, which usually appears strikingly small and thrown into folds, and is deprived of its mucous covering to a greater or less extent. The stomach, if concentrated acid has acted upon it, as a rule is noticeably changed, even in external appearance; the outer surface displays, instead of its natural color, a deep black hue. The tissue of the organ is often in the highest degree tender and friable, and may fall apart when only touched with the forceps; at other times it is tough like parchment. On the inside the walls of the stomach are found to be in all possible stages of disorganization, from simple erosion of the epithelium to perforation, and even to a conversion of the tissues into a blackish-brown, slimy mass. The contents of the stomach, which very frequently, though not always, manifest a strongly acid reaction, consist chiefly of dark masses which resemble coffee-grounds, and which vary both in bulk and in consistence. In less severe cases the discoloration is not so decided, and ulcers are found in varying numbers. In cases of perforation of the stomach the abdominal cavity is more or less filled with

the blackish-brown contents of the stomach, which also usually manifest a strongly acid reaction, and alter the other organs in the abdomen to a variable extent. The convex surface of the liver is sometimes found to be discolored and altered to the depth of several lines. Its appearance has been compared by some to that of a pyogenic membrane,[1] and microscopically the liver-cells are found to be disorganized even to their nuclei. In the intestinal canal—should the acid pass as far down as this—phenomena analogous to those observed in the stomach are to be found. In isolated cases—and then only when the stomach has been perforated—the colon and other intestinal convolutions have been found to be perforated, apparently in consequence of the action (on their external surface) of the acid contents that have escaped from the stomach. Recently the liver has been found in a state of fatty degeneration, the kidneys in that of parenchymatous nephritis. The respiratory and circulatory organs seldom show anything abnormal, nor do those of the central nervous system.

In rare cases the arteries and veins have been found extensively filled with firm clots. The blood is said to show usually a tarry consistence and black color. It has already been noted above that during life its reaction is not acid, and that if an acid reaction be found after death, it is probably to be considered as a cadaveric change.

If death ensues in a later stage of poisoning, cicatrices will be found in different places, and strictures, especially in the œsophagus and stomach. It has already been stated that these develop by preference at certain localities. As regards their structure, they are mostly fibrous, though in a few cases they have been found to contain cartilage. Above the stricture the lumen of the œsophagus is usually dilated, but below, it is strongly contracted. For the rest, in such corpses we find everywhere the indications of a high degree of inanition, such as general lack of fatty tissue, atrophy of the muscles, etc.

The *prognosis* in all cases of sulphuric acid poisoning is doubtful, in many cases absolutely bad.

The *treatment* has for its chief task to render the poison in-

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[1] Case of *Wardell's*, Brit. Med. Jour. Sept. 1869.

nocuous. Though this appears, *à priori*, so simple, and though a whole series of true antidotes are so easily obtainable, we nevertheless cannot count with any assurance upon neutralizing the effects of the poison. The reason for this lies in the facts: first, that this poison is exceedingly rapid in its action; and secondly, that there is such marked difficulty in swallowing. Of course, emetics are not to be thought of in a condition where vomiting belongs among the most prominent symptoms. We can therefore only take into consideration the application of substances which can neutralize the effects of the acid.

There has been a good deal of discussion over the advisability of administering the different alkalies as antidotes; many have even recommended large quantities of pure spring water as the best remedy, basing this advice upon the favorable results which, in a few cases, followed the immediate drinking of plentiful draughts of water,[1] and also upon the assumption that by this means the sulphuric acid is prevented from withdrawing water from the tissues.

In the first place, we must agree with Husemann[2] when he asserts that the nearest remedy is the best. Everything depends on neutralizing the poison with the greatest possible promptness. Every moment of culpable delay is, therefore, to be reckoned as an error. Such alkalies as are to be found in every house—chalk, soap, ashes, or whatever of that nature may come to hand—must be employed at once, while waiting for the prescribed remedies to arrive from the apothecary's. Of the officinal alkalies calcined magnesia is best suited for the purpose. The carbonated alkalies should not be employed where they can possibly be avoided, on account of the active development of gas which follows their administration, and moreover, because they also have a slightly caustic action, and are only converted into sulphates in the presence of large quantities of water.[3]

We do not think it necessary to discuss this question further, since no valid objection can be raised to the employment of

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[1] *Fischer*, Preuss. Vereinszeitung. 1849.

[2] Loc. cit. p 765.

[3] *Luedike*, Ueber die Gegengifte der Schwefelsäure Preussische Vereinszeitung. 1839. No. 45

calcined magnesia, provided it is used at the right time. With regard to the possibility of using the stomach-pump, and its efficiency in sulphoxysm, we can form no reliable opinion, for the want of reported cases on which to base it. We must bear in mind, however, the possibility that the walls of the stomach and œsophagus, which have been softened by the action of the acid, might be artificially perforated by the tube.

The further treatment of a case of poisoning must be purely symptomatic.

CHAPTER II.

POISONING BY HYDROCHLORIC ACID (SPIRIT OF SALT, MARINE ACID, MURIATIC ACID).

Anhydrous hydrochloric acid is at ordinary atmospheric pressures a gas, which when exposed to the air forms a white cloud by combining with the aqueous vapor existing in the atmosphere. The preparations of hydrochloric acid used in chemistry, medicine, and the arts, are aqueous solutions of the acid of varying degrees of concentration and purity; they also develop fumes of hydrochloric acid when exposed to the air. These are in the highest degree poisonous to the respiratory organs of animals, and are also very inimical to plants, the life of which it destroys after twenty-four hours' action even at a dilution of 1 : 20000 (Christison and Turner[1]).

In other respects the action of hydrochloric acid as a poison is entirely analogous to that of the other mineral acids. Its affinity for water is said to be somewhat weaker than that of sulphuric acid, and the intensity of its corrosive action is also said to be somewhat less marked; but we possess very few experimental and clinical data for a comparison of the action of the two acids.

Everything that has been stated about the nature of the

[1] *Christison*, loc. cit.

action of sulphuric acid will apply, with a few modifications, to that of hydrochloric acid. Immediately after the poisoning a few observers (Guérard) have seen hydrochloric acid fumes in the expired breath of the subjects, but at a later period these are no longer to be seen. The urine of men and animals poisoned with hydrochloric acid has been found to be rich in chlorides. The few experiments on animals, which were made some time ago by Sproegel, Courton, Viborg, and Orfila, have afforded scarcely any noticeable results. These experiments were performed on dogs and horses, and in some of them the poison was injected into a vein. Recently no toxicological experiments have been made with the acid.

Cases of poisoning by hydrochloric acid are rare. Up to the present time only about fourteen cases are to be found recorded in all the literature of toxicology.[1] In an etiological connection the easy accessibility of hydrochloric acid, which is much used in the ordinary affairs of life, is of importance. In the majority of the cases known, the poison was taken with suicidal intent; the others are cases of accidental poisoning.

Hydrochloric acid fumes can of course also cause poisoning, when they penetrate in any considerable quantities into the respiratory organs of human beings. This is not unfrequently the case in factories. The poisonous fumes do not produce general symptoms so much as local affections of the mucous membranes with which they may come directly in contact. According to Eulenberg,[2] the use of chloride of sulphur in the preparation of vulcanized rubber affords a favorable opportunity for the development of hydrochloric acid fumes (together with those of sulphurous acid), since the chloride of sulphur decomposes rapidly when in contact with water or atmospheric air.

In the manufacture of bricks, pottery, and glass also, as well as in the making of artificial fertilizers and the like, hydrochloric acid vapors are frequently given off (Eulenberg).

With regard to the quantity of hydrochloric acid required for

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[1] See *Taylor*, loc. cit., who also reports in extenso the cases mentioned by Husemann. Recently cases have been published by *Koeppen*, *Budd*, *Johnson*, *Nager*, and *Paul*.

[2] Loc. cit. p. 531.

the production of dangerous or fatal poisoning, the clinical data at our command are too few to allow a general conclusion to be drawn. From the observations recorded, it appears that half an ounce of the concentrated acid can cause death.

The following table contains the data having a bearing on this point, which are derived from the cases that have been observed up to the present time.

Observer.	Quantity of the Poison taken.	Result of the Poisoning.
Stevenson.	1 wineglassful.	Recovery in 8 days.
Collas.	℥ ii.	Death after a few hours.
Budd.	ʒ i.	Death after 18 hours.
Procter.	℥ ss.	Recovery in 19 days.
Allen.	℥ ii.	Recovery in about 14 days.
Guérard.	ʒ ii.	Death in 8 hours.
Orfila.	℥ iss.	Death after a few days.
Johnson.	1 teaspoonful.	Death in 16 hours.

In the other cases the quantity of the poison taken and the result cannot be accurately ascertained.

The symptoms of hydrochloric poisoning agree with those of sulphoxysm in all essential points.

The local action on the oral and pharyngeal cavities is somewhat less intense in poisoning by muriatic acid, and, according to Paul,[1] the results might be mistaken for diphtheria.

In some of the cases observed, the pains in the stomach and epigastric region were slight, but they were very severe in the throat (Procter, Johnson).

The affections caused by the fumes consist partly in inflammation of the conjunctiva, partly in bronchial and laryngeal irritation, which have nothing distinctive in themselves. The post-mortem appearances in poisoning by hydrochloric acid present no noteworthy differences from those of poisoning by other mineral acids. The treatment must be regulated according to the same fundamental principles laid down for sulphuric acid poisoning.

[1] Bullet. génér. de Thérap. Oct. 1871.

CHAPTER III.

POISONING BY NITRIC ACID (ACIDUM NITRICUM, AQUA FORTIS) AND HYPONITRIC ACID (NITROUS ACID).[1]

Of the various preparations of nitric acid, only three are important from a toxicological standpoint, namely: 1. The officinal pure nitric acid, containing about 28 per cent. of anhydrous acid, colorless, and, at ordinary temperatures, forming no fumes in the air. 2. The crude nitric acid (aqua fortis), which fumes slightly, and, owing to the presence of various other substances, has a yellow color; and, 3. The fuming nitric acid, which is essentially a mixture of nitric and hyponitric acids, has an orange-yellow color, and gives off in the air dense, yellowish-red fumes of hyponitric acid.[2] The only difference in the toxic action of the three is that, in the case of the two last, the presence of the gaseous hyponitric acid frequently causes complications. Moreover, this gas can by itself produce poisoning.

On the whole, nitric acid poisoning also presents so few noticeable differences from sulphuric acid poisoning, that we have scarcely anything to add here, concerning the nature and the symptomatology of the poisoning, to what was said about sulphuric acid. Among the experimental researches we may mention those of Viborg[3] and of Blake.[4]

The former experimented on horses affected with glanders; they recovered after the injection of a drachm of fuming acid into the jugular vein. Blake, after injection of dilute nitric acid into the veins of animals, observed cramps, stoppage of respiration, and rapid lowering of the blood-pressure, accompanied after a few minutes by attempts at vomiting.

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[1] Hyponitric acid and nitric acid are not identical, as appears to be here implied. In the new system in chemistry there is no such thing as hyponitric acid, it being nitrogen tetroxide (N_2O_4); nitrous acid is HNO_2, the corresponding oxide being N_2O_3; (nitrogen trioxide).—TRANSLATOR'S NOTE.

[2] See note by translator, above.

[3] Nordisch. Archiv. für Heilkunde, etc. 1802.

[4] Edin. Med. Journ. 1839.

When nitric acid is brought in contact with animal tissues, the well-known yellow coloration appears which we are accustomed to ascribe to the formation of xanthoproteic acid. This circumstance is sometimes, though not always, in itself sufficient for the differential diagnosis between sulphuric and nitric acid poisoning. The intensity of the action is naturally proportional to the strength of the acid; when this is in a concentrated state, the phenomena it produces are scarcely less violent than those caused by sulphuric acid.

Wunderlich[1] saw one case of nitric acid poisoning take a peculiar dysenteric form, while at the same time the symptoms of acute morbus Brightii were present. A point of especial interest in this case was the complete absence of pathologico-anatomical changes in the small intestine, while the large intestine presented the most intense dysenteric lesions. In discussing this state of affairs, Wunderlich refers to Rokitansky's theory, that dysenteric processes are connected with an acid state of the blood.

In other respects the course of the poisoning, the sequelæ, and the pathologico-anatomical lesions, present the greatest possible similarity with those of acute sulphoxysm.

Though more frequent than poisoning by hydrochloric acid, cases of poisoning by nitric acid, on the whole, occur rarely. In the monograph of Tartra on nitric acid poisoning, which was quoted by Husemann (loc. cit.), but which we unfortunately were unable to gain access to, 56 cases are reported, which were all that were recorded during a period of 400 years. In the more recent literature only 20 or 30 cases are mentioned.[2]

Opportunities for poisoning with nitric acid are plenteously afforded in ordinary life, since this acid also finds manifold applications in the trades and manufactures.

Of the cases observed up to the present time, the larger proportion are cases of suicide; one was a case of murder (reported by Cazaulvieilh).[3] The rest belong in the catalogue of accidents.

[1] Ueber einige Wirkungen concentrirter Salpetersäure auf den menschlichen Organismus. Academ. Programm. 1856.

[2] Cf. also *Taylor*, loc. cit.

[3] Annal. d'Hygiène publ. 1836. Murder of a new-born child by its mother. We may

On account of the small number of the available observations, the fatal dose cannot be determined with any more certainty than in the case of hydrochloric acid. The treatment is the same as for sulphuric acid poisoning.

Poisoning by nitrous acid may be combined with the ordinary poisoning by nitric acid (when considerable quantities of fuming nitric acid are used), and it then modifies to some extent the clinical picture of the latter; or it may occur independently in consequence of the inhalation of larger or smaller quantities of the poisonous gas, which is developed under many different conditions from nitric acid and other chemicals in chemical laboratories, manufactories, telegraph offices, and the like (cf. Eulenberg on this point, loc. cit.). Usually it is the breaking of large vessels filled with fuming nitric acid which furnishes the opportunity for the escape of the gas. It has recently been asserted that the gas frequently accumulates in factory-rooms, and especially in anilin and nitro-benzin factories. To ascertain the action of this gas, Nysten (loc. cit.) made some experiments, which have recently been extended by Eulenberg (loc. cit.). Nevertheless, we are still considerably in the dark as regards the essence of the poisoning, and are unable as yet to determine positively how much of its action is to be ascribed to local influence of the gas, and how much to its remote action. Special stress has been laid upon the black color of the blood, in which, as Eulenberg thinks, nitrogen compounds have formed.

The local effects of the gas, which is exceedingly irritating to the air-passages, are very prominent in all cases. They consist in a severe burning sensation in the mucous membrane of the nose, a strangling, suffocating feeling in the windpipe, severe cough (sometimes with bloody expectoration at the very beginning), oppression of the chest, dyspnœa, and the other symptoms of suffocation.

Undoubtedly death by suffocation may be provoked immediately and solely by the local action of the gas upon the air-passages and the lungs, if it is inhaled in sufficient quantities.

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class with it also the case in which the poisoning was effected by pouring the acid into the external ear (*Taylor*, loc. cit. II. p. 59).

In some cases the violence of the symptoms abated somewhat after a time, but in the course of a few days deep-seated changes in the organs of respiration (pneumonia? bronchitis) gradually developed, and finally resulted also in death. The question whether the alteration of the blood produced by the gas can also produce death by asphyxia, must be left open until further investigations warrant more certain conclusions.

The occurrence of general symptoms is, however, positively established; disorders of the organs of digestion (vomiting), as well as of the nervous system, have been observed. Still, it must not be forgotten that probably, as a rule, a certain amount of the gas is swallowed, and reaches the stomach, where it can also produce local symptoms.

Prolonged exposure to the action of small quantities of the gas gives rise to chronic forms of laryngitis and bronchitis, and sometimes also to conjunctivitis.

At the post-mortem examinations, as a rule, only a more or less marked alteration in the organs of respiration (hyperæmia, swelling, ecchymosis, œdema of the lungs), and the above-mentioned dark color of the blood, can be positively demonstrated.

The treatment of this form of poisoning must be limited to purely symptomatic procedures, after the cause has been removed.

CHAPTER IV.

POISONING BY HYDROFLUORIC ACID.

Hydrofluoric acid (HFl) is a colorless liquid which gives off corrosive vapors at ordinary temperatures. In consequence of its great affinity for silica, it attacks glass readily and even dissolves it. It is the strongest of all the corroding agents now known to us.

Although the corrosively poisonous action of its fumes and its aqueous solutions have long been known (the Belgian chemist Louyet is said to have died from inhaling its fumes),[1] and the

[1] *Husemann*, Toxikologie. p. 792.

substance has, moreover, been somewhat extensively used for etching glass, yet hydrofluoric acid did not assume practical importance in a toxicological point of view until the year 1873, when the first case of fatal poisoning by it was observed.

On the external skin the acid produces suppurating ulcers, which heal slowly; its action is attended by intensely severe pain. In the case just mentioned, which was reported by King,[1] a toper, forty-six years of age, swallowed half an ounce of the acid (concentration not mentioned), and died thirty-five hours after taking the poison, the symptoms being violent vomiting speedily followed by collapse. It was especially noted that the motion of the heart ceased before the respiration.

At the autopsy, in addition to other points, an acid reaction of the blood, a separation of the epithelium in the cavity of the mouth and the œsophagus, and a dark red discoloration of the mucous lining of the stomach, were noticed. The contents of the stomach were thick and black.

CHAPTER V.

POISONING BY SULPHUROUS ACID (ACIDUM SULPHUROSUM).

Sulphurous acid (SO_2)[2] belongs among the strongly irritating gases. It has a pungent, suffocating odor, an acid reaction, is readily soluble in water, but in aqueous solution changes immediately into sulphuric[3] acid. Since it is developed in large quantities in a large number of technical processes during which it is partially diffused in the air of the factory and workrooms, it might be supposed that it must frequently give rise to serious cases of poisoning. Practical experience proves, however, that

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[1] Reported by *Th. Husemann*, in Virchow and Hirsch's Jahresber. 1873. I. 358.

[2] According to the new nomenclature SO_2 is sulphur dioxide or sulphurous oxide, and this oxide, combined with water (H_2SO_3), constitutes sulphurous acid. The author throughout this chapter applies the term sulphurous acid to the sulphur dioxide.—TRANSLATOR'S NOTE.

[3] See *Eulenberg* on this point: Schädliche und giftige Gase; and *Hirt*, Krankheiten der Arbeiter. I.

the reverse is true, and we must unquestionably class sulphurous acid gas among the toxicologically unimportant substances.

Recently Eulenberg (loc. cit.) and L. Hirt (loc. cit.) have instituted investigations to determine the nature of the action of sulphurous acid. The results obtained by the latter author especially are of great theoretical interest. He found that the gas, when inspired in different degrees of concentration by animals, produced partly local and partly remote effects, the latter being evidently consecutive to the absorption of the poison into the blood. The pause in respiration during expiration—which invariably followed inhalation of the poisonous gas through the mouth or nose, persisted for from twenty-five to thirty hours, and sometimes recurred again and again—must be regarded as a reflex phenomenon caused by the irritation of the sensory nerves of the nasal mucous membrane. It did not appear when the sulphurous acid was conducted through a canula below the larynx directly into the trachea. The poison, moreover, produced labored, dyspnœic breathing, diminution in the frequency of the respiration, and finally stoppage of respiration by paralysis of the respiratory centre. Animals in which the vagi had been divided bore more sulphurous acid than uninjured animals.

Hirt observed inflammation of the lungs after the inhalation of concentrated fumes. The action of the poison extends also to the innervation of the vessels and the heart. The vaso-motor centre is at first excited, and afterwards paralyzed (decrease of arterial blood-pressure) by small doses ; large doses cause paralysis at once. The effect on the heart, in Hirt's opinion, is due to the direct injurious action of the poison on the cardiac muscle. In the animals poisoned with sulphurous acid, the blood showed no notable alteration.

It is evident from these statements that it is still doubtful how large a proportion of the entire effect produced by sulphurous acid on the respiration and circulation is attributable to its local action, and how much to a remote action. For the present we must rest contented with our ability to demonstrate the existence of both kinds of action.

Very few cases of acute and fatal poisoning by sulphurous

fumes are on record, and even they belong to earlier times.[1] Death ensues with symptoms of severe asphyxia.

The disorders observed among workmen who are exposed to an atmosphere saturated with sulphurous acid fumes, are, as a rule, trifling—if the proportion of the poisonous gas in the air is within the ordinary limits—namely, from 2 to 4 per cent. The difficulties consist chiefly in anomalies of digestion.[2] Hirt denies absolutely any special tendency to serious affections of the lungs among such persons. When the atmosphere contains from 5 to 7 per cent. of the gas, a prolonged stay in it usually produces severe bronchial irritation—long-continued fits of coughing, and also conjunctivitis—phenomena which disappear only after removal from the poisoned atmosphere.

B. *Vegetable Acids.*

CHAPTER VI.

POISONING BY ACETIC ACID (ACIDUM ACETICUM).

In a diluted form (vinegar), acetic acid, as is well known, finds very extensive use as a condiment with various kinds of vegetable and animal food. Used in proper quantities, vinegar is rather beneficial than hurtful to health: an excessive use of the acid, however, cannot be borne long without injury.

Concentrated acetic acid, and especially the anhydrous or so-called glacial acid (acidum aceticum glaciale) are corrosive poisons, the action of which is but little inferior to that of the weaker mineral acids. Acetic acid ($C_2H_4O_2$) is volatile, and its fumes have a peculiar, pungent odor, which in a slight degree is possessed also by vinegar. It is miscible in all proportions with water, and with the bases forms different series of salts. When brought in contact with the constituents of the animal body, it

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[1] Cf. *Husemann's* Toxikologie on this point.

[2] The inhalation of sulphurous acid for a short time, and in small quantities, is said to cause an increased appetite. Hirt tested this action upon himself.

asserts its chemical affinities by combining with the available water and with the free bases, or those which are in combination with carbonic acid ; it also unites with the albuminoid substances. Even before it is absorbed by the mucous membranes, a portion of the free acid is fixed by the processes just mentioned, while the remainder, which is taken up by the blood, undergoes similar changes with the constituents of that fluid. The local corrosive action of the acid is incontestably also to be referred to its affinity for water, bases, and albuminous substances. It has not yet been ascertained whether appreciable quantities of the acid may be introduced into the blood by breathing the fumes. These fumes, however, in proportion to their concentration, act as a more or less intense irritant to the mucous coats of the air-passages. It has been demonstrated by the researches of Krause and Bobrik,[1] that acetic acid can also make its way into the blood through the uninjured epidermis. Bobrik observed in himself a thread-like and noticeably retarded pulse, and a decrease of $\frac{3}{4}$° C. (1.35° Fahr.) in the temperature of the body after a foot-bath consisting of three bottles of strong vinegar. With regard to the behavior of acetic acid in the blood and tissues, and the form in which it is eliminated, there are as yet no accurate researches on record. Still, we may assume that the blood of living animals cannot contain free acetic acid for a long time any more than it can contain other free acids. The blood of animals poisoned by acetic acid has never been found acid. It is, moreover, highly probable that the acetates, like other salts formed by the organic acids, are changed into carbonates in the organism.

As early as 1827, Woehler[2] proved that free organic acids (oxalic, tartaric) are excreted in the urine of the dog ; the crystalline lime salts formed with these acids were deposited on the walls of the urine vessels. When, however, alkaline salts formed with vegetable acids were administered to the animal, carbonic acid appeared in the urine instead of the vegetable acid. With regard to the point where the conversion of the vegetable acid into carbonic acid took place, Woehler only showed that the stomach is not instrumental in effecting the change. The vomit of the animals, even several hours after the administration of the vegetable salts, did not have any alkaline reaction.

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[1] Acida et vegetabilia et mineralia qualem vim atque affectum habeant, etc. Diss. Königsberg. 1863.

[2] Hufeland's Journal d. prakt. Heilkunde. 1827. 64. Vol. I. St. p. 86.

The action of acetic acid on the animal organism agrees entirely in its essential points with that of other strong acids. Its behavior towards the various chemical constituents of the body has been determined accurately by the researches of Mitscherlich,[1] Lehmann,[2] and others. Since the physiologico-chemical results have no special bearings on toxicology, we think we may pass them over here. Among other things, it was found that the red blood-corpuscles were dissolved by acetic acid, and attempts have been made to explain certain effects, *e. g.*, decrease in the temperature of the body and frequency of the pulse, (Heine[3]) by this fact, though the proof is still wanting that the solution which is observed under the microscope also occurs in the living blood.

Munk and Leyden[4] assert that tartaric and oxalic acids dissolve the red blood-corpuscles in the living blood. They do not mention acetic acid in this connection.

Goltz and Bobrik have shown that acetic acid (as also other vegetable acids, tartaric, citric, etc.) exerts a specific influence on the heart of frogs and warm-blooded animals independently of any action on the nervous system. In the former, after the application of the acid in various ways, the number and energy of the heart-beats were diminished until they stopped completely. In rabbits also a stoppage of the heart for several minutes could be effected by injecting the acid into a vein. Bobrik demonstrated on himself the action which the acid exerts in diminishing the temperature and retarding and weakening the pulse.

It is a specially interesting point, that, according to Bobrik's researches, dilute mineral acids have just the contrary effect, inasmuch as the frequency and strength of the pulse is never lessened by them, but is, on the contrary, regularly increased.

While, in accordance with Bobrik's experience, we must admit that vegetable acids, and especially acetic acid, have a specific action upon the heart, some more recent observations and researches made by Heine (loc. cit.) on men and animals make

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[1] De acidi acet., oxalic, etc. etc. affectu. Berolin. 1845.

[2] Med. Centralblatt.

[3] Virchow's Archiv. XLI. 1868.

[4] Berlin. klin. Wochenschrift. 1864. Nos. 49 and 50.

it probable that the functions of the nervous system are also affected by large doses of acetic acid. Heine observed in animals periodical tetanic spasms, in men general tremor of the muscles, shivering and exceedingly rapid collapse. The last-mentioned symptom might, it is true, have been due to anomalies in the circulation, to great feebleness in the action of the heart.

The rapid death of animals, into whose blood considerable quantities of concentrated acid have been injected, is evidently due to the alterations in the blood caused by the powerful chemical agent.

The local action of acetic acid presents but little that is characteristic. Its intensity is in direct ratio to the concentration of the acid. While diluted acid produces only severe burning sensations and temporary hyperæmia, stronger solutions cause vesication and, when applied for a long time, ulcers and eschars. Selinsky[1] asserts that he produced artificial croup membranes by injecting acetic acid into the air-passages. On the mucous coats of the intestinal canal it effects exactly the same alterations as do the weaker mineral acids.

The entire number of cases of acute acetic acid poisoning, hitherto recorded in medical literature, only amounts to six. Of these two resulted fatally (Heine and Hergott) from the injection of liquor Villati into suppurating wounds.

Heine has proved experimentally that the acetic acid is in fact the toxic agent in the liquor Villati. This solution consists of half an ounce each of cupric and zincic sulphates, seven drachms of solution of subacetate of lead, and six and a half ounces of acetic acid. A dose of acetic acid corresponding to the quantity of the acid contained in the liquor Villati killed a dog in two minutes, while a corresponding amount of liquor Villati, from which the acetic acid only was omitted, proved harmless.

The cases of Orfila,[2] Barruel,[3] and Birkett[4] were attempts at suicide, and that of Melion[5] resulted from an accidental exchange of the acid with a medicine. Of these four cases two terminated fatally.

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[1] Petersb. med. Zeitschrift. VI. 1864.
[2] Toxikologie. I.
[3] *Husemann*, Toxicologie.
[4] Lancet, 1867
[5] Frank's Magaz.

All the handbooks also mention a chronic form of acetic acid poisoning, which is said to occur sometimes as the result of the excessive use of vinegar by hysterical persons, or by women who take it for the sake of obtaining a pale complexion. This form is said even to lead to phthisis. We have been unable, however, to discover any detailed observations of such chronic poisoning.

Finally, a prolonged stay in the rooms of vinegar distilleries, or vinegar factories, is said also to exert an injurious influence on the health (to predispose to phthisis). The workmen occupied there are said to suffer not only from the pungent acetous fumes, but also from the lack of oxygen in the atmosphere; in the production of acetic acid the oxygen used is taken exclusively from the surrounding air. On this point also reliable individual observations are lacking.

It is impossible to determine what constitutes a poisonous or fatal dose on account of the small number of recorded cases, which are, moreover, very incomplete in regard to the quantities of the acid taken, the degree of concentration, etc. That diluted acetic acid can be taken in large quantities without injury is proved by daily experience.

The symptoms after poisoning by acetic acid per os consist in severe burning pains, which supervene immediately after taking the acid, and extend to the stomach and abdomen, dysphagia, bloody vomit, diarrhœa, to which, in the more serious cases, the symptoms of a more or less severe collapse are added. Birkett's case (loc. cit.) was notable from the fact that a good deal of the acid flowed into the air-passages, and provoked violent symptoms of suffocation, which, however, were fortunately relieved by timely tracheotomy. In the case described by Heine (loc. cit.), in which liquor Villati was injected into a resection wound on the ankle, which was healing badly, and was becoming covered with croupous membranes, the injection was immediately followed by bleeding from the wound, and violent pains in it. These were soon followed by death-like pallor, trembling of the entire body, with great chilliness, and a very rapid and weak pulse. The patient died in a few hours from rapidly increasing collapse. In Hergott's case, nausea and vomiting

immediately followed the injection, and death also ensued in a very short time.

In chronic acetic acid poisoning, progressive deterioration of the nutrition and general emaciation are said to occur in consequence of the disorders of digestion.

Respecting the post-mortem appearances and the treatment of acetic acid poisoning, we have nothing to add to what has already been said concerning poisoning by the other acids. The odor of acetic acid can, of course, serve as a foothold in the diagnosis of doubtful cases.

CHAPTER VII.

POISONING BY TARTARIC ACID (ACIDUM TARTARICUM) AND CITRIC ACID (ACIDUM CITRICUM).

The effects of both of these acids, which in the chemically pure state are crystalline, and readily soluble in water, correspond in all respects with those of acetic acid. Hence, an extended notice of them is superfluous.

Several cases of poisoning, some of them fatal, have resulted from tartaric acid, which is used very extensively in every-day life as a household medicine and in technical applications.

CHAPTER VIII.

POISONING BY OXALIC ACID.

Oxalic acid ($H_2C_2O_4$) indisputably occupies the first rank among organic acids in a toxicological point of view, on account both of the intensity of its action and of the number of cases of poisoning caused by it.

Besides the free oxalic acid, which is crystalline in form, and readily soluble in water, the potassium oxalate, or salt of sorrel of commerce, is the only preparation of oxalic acid which is of

importance as a poison. Its action is essentially the same as that of the free acid.

This acid possesses in a high degree the caustic and corrosive action on the tissues of the animal organism which is common to all acids, but, in addition to it, produces also very decided effects on the nervous system, which modify considerably the general clinical picture of the poisoning.

As regards its corrosive action, we may content ourselves with referring to the detailed description given of this action in the case of sulphuric acid. The corrosive action of sulphuric acid is, however, somewhat more intense than that of oxalic acid.

The action of oxalic acid on the nervous system has been explained in various ways.

Onsum [1] is of the opinion that oxalic acid, after entering the blood, combines with the lime salts in that fluid, to form the insoluble oxalate of lime, which causes death by clogging the capillary vessels of the lungs. This view is warmly combated by Cyon,[2] who has tried to prove that oxalic acid is a heart-poison. Still Cyon's experiments are too few in number to warrant a positive conclusion regarding the nature of the remote action of oxalic acid, though Onsum's view has hardly any followers at present. Buchheim [3] assumes, in addition to the corrosive action of oxalic acid, a general action on the heart and the nervous system, which also belongs to its soluble compounds. He calls attention also to the high degree of diffusibility which is characteristic of oxalic acid and its soluble compounds; in consequence of this property the oxalic acid compounds can be given in small doses for a long time without injurious results, since they are eliminated in the urine almost immediately after being introduced into the system.

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[1] On the toxic action of baryta and oxalic acid compounds. Virchow's Archiv. Vol. 28. p. 233 (1863).

[2] On the toxic action of baryta and oxalic acid compounds. Arch. f. Anat. u Physiol., by DuBois and Reichert. 1866. p. 196.

[3] Arzneimittellehre. II. Ed. p. 189. Ueber den Uebergang einiger organischen Säuren in den Harn. Arch. f. physiol. Heilkunde. 1857. *Pietrowski*, Dissertation. Dorpat.

We are indebted to Christison and Coindet[1] for very thorough experimental researches on the action of oxalic acid; their results, however, differ in no respect from those just indicated.

In Germany cases of poisoning by oxalic acid occur rather infrequently, but in England they constitute no small proportion of the cases of poisoning observed annually. Out of 527 cases of poisoning occurring in the years 1837–1838, in England, 19 were caused by oxalic acid.[2] As a rule, it seems to have been used with suicidal intent. Several cases of accidental poisoning have occurred in consequence of the oxalic acid being mistaken for magnesium sulphate, tartaric acid (Seidlitz powder), cream of tartar, and the like. Attempts at murder with oxalic acid have also been made in England, though they were thwarted by the intensely acid taste of the poison, which it is difficult to mask.

Thudichum[3] has attempted to settle by experiment the question whether it is possible to poison a person with oxalic acid without his knowledge. He found that even doses of ten grains, which is not really a poisonous dose, although greatly diluted and disguised with various substances (oatmeal gruel, etc.), produced an unendurable flavor that manifested itself immediately, and left behind for some time a feeling of the teeth being "set on edge."

From the literature of the last thirty years, which we have had at our disposal, we have collected 22 cases of oxalic acid poisoning. Of these 19 occurred in England, and 3 in France and Germany. Twelve terminated in death, and ten in recovery. In eight cases suicide had been attempted.

The fatal dose of oxalic acid cannot be certainly fixed upon. Death has been known to follow the administration of two drachms, but recovery has resulted after a half ounce or more was taken. It makes quite a difference whether the poison is taken in the solid form or in a more or less concentrated solution.

We will only discuss here those symptoms of oxalic acid poisoning which relate to the so-called constitutional action of this substance, since the local phenomena are the same as those

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[1] Edinb. Med. Journ. Vol. XIX. 1823.

[2] *Husemann*, loc. cit. p. 353.

[3] Med. Times and Gazette. April, 1860.

caused by sulphuric acid. Apart from a more or less marked shortness of breath, which, though described by certain authors as characteristic of this form of poisoning, may really be due to local disturbances, and are known to occur in poisoning by other acids, the symptoms which indicate an affection of the nervous system are principally located in the sensitive and motor sphere of the same.

Formication, both on the trunk and on the extremities, numbness and anæsthesia of the finger-tips, dragging pains in the back and lower extremities, tonic and clonic spasms, have been quite often observed, and death frequently ensued with tetanic paroxysms. Affections of the kidneys also, similar to those which occur in the case of poisoning by vegetable substances—namely, pains in the region of the kidneys and loins, extending toward the extremities, with painful urination—were observed by Christison and Webb,[1] but at the same time it was particularly noticeable that the affection of the stomach was slight and evanescent or entirely absent. Perhaps these phenomena are connected with the rapid elimination of the oxalic acid compounds demonstrated by Buchheim.

The course is sometimes extremely violent, causing death in a few minutes, and sometimes more retarded and chronic.

Recovery may be preceded by the same sequelæ as are met with in sulphoxysm and other analogous venenations.

On reading the accounts of many cases of oxalic acid poisoning, the general impression left is that there is very little constancy in the phenomena and symptoms, and that both the local and the constitutional manifestations appear in the most manifold combinations, the exact description of which would be synonymous with a complete report of all the cases observed. We are unable to name a single really pathognomonic symptom of oxalic acid poisoning.

The pathologico-anatomical lesions also present nothing that is characteristic. When dilute solutions of the acid have been used as the poison, anatomical changes in the corpse may be altogether wanting.

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[1] *Husemann*, loc. cit.

In the treatment of oxalic acid poisoning the preparations of lime constitute the best antidote, because of the insolubility of the oxalate of lime, but magnesia may also be used, and in case of necessity chalk-water, egg-shells, and the like may prove useful. Recently Husemann[1] has recommended sugar-lime as a suitable antidote. He has obtained experimentally with this substance very favorable results in carbolic acid poisoning. He remarks especially that the quantity of lime required to neutralize the acid can hardly be administered in the form of lime-water, and that the use of the carbonate of lime is inconvenient on account of the voluminous disengagement of carbonic acid. The alkalies are of course counterindicated, since it is well known that their combinations with oxalic acid are not only readily soluble in water, but are also themselves extremely poisonous substances.

THIRD DIVISION.

Poisoning by Alkalies, Earths, and their Salts.

CHAPTER I.

POISONING BY AMMONIA AND SAL AMMONIAC.

Aqueous and gaseous caustic ammonia (water of ammonia, ammonium carbonate and chloride (sal ammoniac) are the few ammonia compounds which are of importance from a toxicological standpoint.

The ammonia fumes, which escape not only from aqueous solutions of the free base, but also from those of the carbonate, have a characteristic, pungent, unpleasant odor. They are

[1] Deutsche Klinik. 1870, 1871. Unfortunately this antidote up to this date has not been adopted into the pharmacopœias, a fact which it is well to bear in mind in prescribing for an urgent case of poisoning.

colorless and not combustible in the air. The other salts have no specially characteristic external properties.

The absorption of the ammonia salts into the animal organism takes place in the case of the volatile compounds both through the organs of respiration and also through all the membranes and surfaces of the body through which processes of diffusion can occur. The non-volatile salts can, of course, only be absorbed through the latter.

The elimination of the ammonia compounds and their behavior while in the body have frequently been the subject of elaborate investigations.

Various authors state that after the administration both of free ammonia and of the salts of this base, they have frequently detected the gaseous ammonia in the expired air, over and above the small quantities which are said to be normally present in the expired breath of animals and men. The statement has been positively refuted by some recent researches which were made on rabbits and cats by Schiffer[1] and also by Lange[2] under our own supervision.

Elimination through the lungs does not occur even when the elimination in the urine is prevented by ligation or removal of both kidneys.

It can hardly be assumed that the human organism would act differently in this respect, though the direct proof can only be furnished for the above-named species of animals.

The elimination of ammonia in the perspiration has not yet been demonstrated experimentally, although Castan[3] has recently declared that he smelt the gas in the cutaneous excretion of a person poisoned by ammonia. Lohrer[4] made, under Buchheim's direction, some experiments on himself and on dogs, to determine the passage of the ammonia compounds into the urine, which led him to the conclusion that all the different salts of this base leave the organism in the urine after varying periods of time. However, these results still require confirmation, inas-

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[1] Berlin klin. Wochenschr. 1872. No. 42.

[2] Inau.-Diss. Dorpat. 1874. und Archiv f. experim. Path. u. Pharmak. II. 1874.

[3] Montpellier med. 1870. cit. in Jahresber. of Virch. and Hirsch. vid. Hus.

[4] Inaug.-Dissert. Dorpat. 1862.

much as there is reason to doubt the accuracy of the Neubaur-Schloesing method for determining the presence of ammonia which was used by Lohrer.[1] Lange (loc. cit.) has sought in vain for free ammonia in the blood of animals, into which large quantities of ammonia compounds had been injected during life by the jugular vein. The ammonia reaction only showed at a temperature at which the decomposition of the albuminoid constituents of the blood might have produced fresh ammonia. According to the recent researches of Knieriem,[2] the major part of the ammonia taken into the system is transformed into urea, in which form it appears in the urine.

The general phenomena occurring after the absorption of ammonia compounds are common to all the combinations of this base, but some of them are also characterized by an exceptionally severe local action. In the case of the gaseous combinations this local action affects the organs of respiration, while, where an aqueous solution of caustic ammonia is swallowed, the mucous coats of the digestive tract are attacked. The caustic action of the latter manifests itself also when it is applied to the external skin.

In their nature the local actions of the gaseous preparations and of the aqueous solutions of ammonia are closely related; at least it is difficult to perceive why gaseous ammonia, as well as the solution, obeying its affinity for water, should not extract from the tissues that substance which is their most important constituent.

The local effects of ammonia on organs containing nerves are, under all circumstances, coupled with the phenomena of intense irritation of the sensitive nerves, which manifests itself not only by violent pains, but also (in the air-passages) by energetic reflex action. Thus ammonia fumes, when at all concentrated, produce at once, by reflex action, convulsive expiratory movements, fits of coughing, such as occur in animals after central irritation of the nervus laryngeus superior, and spasmodic closure of the glottis. Whether or not these phenomena of intense irritation

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[1] See *Lange*, loc cit.

[2] Zeitschr. f. Biologie. 1875.

are also connected with the chemical action of the ammonia (abstraction of water) cannot for the present be decided.

In other respects the local phenomena are similar in character to the effects produced by other inflammatory irritants. The assertion that ammonia, when applied either in fluid or gaseous form to the mucous membrane of the larynx and trachea, produces croupous pseudo-membranes, which are regarded by Reitz[1] and Oertel[2] as the product of a genuine croupous inflammation, has recently been subjected to a thorough test by Heinrich Mayer.[3] He came to the conclusion that the products of the inflammation excited in the air-passages by the poison present at the outside only a macroscopic resemblance to croup membranes, but otherwise lack all the essential characters of that form of exudation. The affection is a simple inflammation.

The study of the phenomena which ensue after the absorption of poisonous quantities of ammonium compounds establishes beyond question the fact that all the salts of this base exert the same action—varying only in intensity—on the organs of the nervous system and of the circulation. Lange and the writer have proved experimentally that even ammonium chloride does not, as some authors assume,[4] form an exception to this rule; on the contrary, it is distinguished by an especially energetic action upon the nerves. The most striking phenomena are the disturbances of respiration and of the voluntary movements. The former consists in an enormous increase in the frequency of the respiration, which succeeds a short pause in the breathing that occurs immediately after the administration of the poison; we ascribe it to a central irritation, by the poison, of the respiratory tract in the medulla oblongata. This irritation is so intense that it even leads to a marked acceleration of the breathing in animals whose nervi vagi were previously severed. This fact is of practical significance, since it affords a theoretical basis for the employment of injections of ammonia, which have been recommended in the treatment of certain forms of asphyxia.

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[1] Wiener Sitzungsbericht. Vol. LV. 2. 1867.

[2] Deutsches Archiv f. klin. Med. VIII. 1871.

[3] Arch. d. Heilkunde. 1873. VI. 512.

[4] *Buchheim*, Arzneimittellehre. II. ed. p. 175.

The tetanic convulsions provoked by the ammonium compounds proceed from the spinal cord. This is evident from the fact that they occur also in animals in which the cervical marrow has been severed between the atlas and axis, and which are kept alive by artificial respiration.

The action which all the ammonium compounds exert on the circulation consists in an enormous increase in the blood-pressure. This was first observed by Blake,[1] and has recently been investigated by Lange and the writer (loc. cit.), and also by Funke and De Ahna.[2] The alterations which the frequency of the pulse undergoes under these conditions are inconstant and unimportant. Experiments on animals, after division of the cord in the cervical region, showed that the increase of pressure could not be referred to some central influence, emanating from the medulla oblongata. Very large doses diminish the blood-pressure so much that the animal succumbs, and at the same time they deprive the respiratory centres of their excitability and vitality.

The phenomena described, so far as they relate to the respiration, are most intense, and are developed most rapidly, when they are provoked by the carbonate or by free ammonia; after the administration of ammonium chloride, on the other hand, the action upon the blood-pressure is most prominent, though the disturbance of the respiration is also sufficiently marked. In both respects ammonium sulphate has the weakest action of all the preparations. L. Hirt[3] has recently investigated the alterations which the blood of animals undergoes after the inhalation of large quantities of ammonia fumes. He found that the blood really does assume a dark, brownish-red color, but when exposed to the atmospheric air it immediately becomes bright red again. The results of the spectrum analysis are in every respect the same as those given by normal blood. The red blood-corpuscles are only destroyed when ammonia gas is introduced in large quantities into the blood.

The toxic action of the ammonium compounds consequently

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[1] Edinb. Med. Journ. 1847.

[2] *Pflueger's* Archiv. IX.

[3] Krankheiten der Arbeiter. I. p. 93.

consists essentially in local phenomena of irritation, and in a general action on the nerve-centres and the circulation.

The non-volatile ammonium salts only cause disorders in the alimentary canal when they are ingested in large quantities and in a highly concentrated form.

Cases of ammoniacal poisoning arise as well from the manifold applications of the ammonium compounds, in trades and manufactures, as from accident; in rare cases they are suicidal in nature. Hirt has proved (loc. cit.) that the injurious action of ammonia fumes, which are developed incidentally in many chemical works, has been greatly over-estimated, since tolerably large quantities of it can be inhaled by the workmen without special injury to health. Very violent symptoms of poisoning are only provoked by prolonged inhalation of concentrated ammonia fumes.

Very complete data respecting the development of ammonia fumes are given by Eulenberg (loc. cit.). We will allude here only to the presence of this noxious gas in sewers and privy vaults, because it explains the locally irritating action which the gases produced in such places frequently exert. The degree of concentration which ammonia fumes can attain in badly appointed privies is often so great, that under certain circumstances they may even cause serious poisoning.

Medical literature contains only a few cases of poisoning by gaseous ammonia. In a case reported by Tardieu,[1] a physician, while in an epileptic fit, was poisoned with ammonia by a porter; the latter, in the attempt to bring the sufferer to his senses, having held a handkerchief, soaked in ammonia, to his nose, and thrust it into his mouth. The case ended fatally, and Nysten found at the autopsy excessive croupous (?) inflammation of the air-passages.

In two other cases of poisoning by ammonia fumes, the victims were druggists, and in both the poisoning was brought about in the same way—namely, by the breaking of large flasks filled with ammonia.[2] Quite recently a similar accident occurred

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[1] Étude medico-legale sur l'empoisonnement, etc. p. 285.

[2] *Souchard*, Ann. d'hyg. publ. 1841. I. p. 219.

with an ice-machine, which proved fatal to a workman who was tending it.

The careless use of water of ammonia to revive fainting, drunken, or asphyxiated persons, also sometimes causes poisoning. Besides the above-mentioned case of Tardieu's an analogous case, which, however, terminated in recovery, is recorded by Delioux de Savignac,[1] while a third, in which ammonia was persistently held under the nose of an epileptic, terminated in death.[2]

The cases of poisoning by solutions of ammonia are somewhat more numerous. They were mostly the result of accident and of inadvertent medicinal use of the drug. With one exception, in all the cases belonging in this category, which are recorded in medical literature, the ammonia was taken internally. The exception is a case reported by Paget,[3] in which a dilute solution of caustic ammonia was injected into a nævus. The patient, a child two years of age, died in convulsions immediately after the injection.

Regarding the quantity of ammonia or of ammonium salts necessary to produce poisoning and death, nothing positive can be stated; on the one hand, because the observations made on human beings are too few in number, and on the other, because in the individual cases the quantity of the poison used can seldom be determined. We will not attempt, therefore, to give any figures on this point.

In the majority of cases the poison used was caustic ammonia; cases of poisoning by the carbonate and chloride are rare. The following small table of statistics, in which the writer has inserted all the cases that are to be found in the medical literature at his command, contains all the points that can be educed from this available material.[4]

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[1] *Castan*, Montpell. med. 1870.

[2] Diction. encyclopæd. des scienc. med. I. Ser. III. 1869.

[3] *Christison*, loc. cit. 233.

[4] The cases are collected from Schmidt's Jahrbuch, the handbooks on toxicology of Tardieu, Taylor, and Christison, the Dictionnaire encyclopédique des sciences médicales; the sources of some are mentioned above.

Form in which the poison was taken.	Men.	Women.	Children.	Result.		Occasion.				Sum.
				Recovery.	Death.	Accident.	Medical Use.	Suicide.	Murder.	
1. Caustic ammonia.										
a) inhaled.	5	..	..	3	2	4	1	..	..	5
b) internal.	19	8	..	12	15	14	3	9	1	27
c) subcutaneous.	..	..	1	..	1	..	1	..	..	1
2. Ammonium carbonate.	1	1	2	2	2	1	1	1	1	4
3. Chloride.	1	..	..	1	..	1	..	..	..	1
Total	26	9	3	18	20	20	6	10	2	38

If it be at all allowable to attempt the production of a general clinical picture from the symptomatic material furnished by the few cases of ammonia poisoning in man hitherto reported, special stress must be laid on the following principal features. In most cases the phenomena produced by the local action of the poison are much the more prominent, those symptoms which, as we have learned from experiments on animals, depend upon the constitutional action of the ammonia being rarely very markedly developed. Thus ammonia poisoning presents an undeniable similarity to the intoxications provoked by the other corrosive poisons. The amounts necessary to produce the general toxic action in men seem to be pretty large. It may be that the local phenomena excited by caustic ammonia render the absorption of large quantities into the blood impossible.

As with all corrosive poisons, so in poisoning by ammonia, the reaction of the organism is immediate, whether the toxic action be produced by the penetration of the fumes of the base into the air-passages or of the aqueous solution into the intestinal canal.

Very severe pains in the mouth, pharynx, larynx, and along the trachea usher in the symptoms, and excite the active reflex action. Not infrequently the intensity of this irritation of the sensitive nerves is so great that it causes complete insensibility, which lasts, however, only a short time.

When the gas is inhaled, the organism responds by spasmodic expiration and temporary closure of the glottis, and thus

prevents the admission of more of the irrespirable substance. When the poison is taken in the fluid form, whether it be taken accidentally or intentionally, the intense pain, as a rule, causes it to be spat out immediately. Even the firmest determination to commit suicide is paralyzed by the physical pain, which drives all other considerations out of the mind.

The disturbances of respiration are not confined to the cases in which the poison has been inhaled; they are also observed after it has been taken by the mouth more frequently than they are in the case of any of the other poisons. The reason for this is either because the solution, while in the oral cavity, evolves fumes in considerable quantities, which find their way into the neighboring air-passages, or because some of the solution itself gets into these passages.

After the cessation of the spasmodic reflex movements, a persistent and violent burning pain, which is experienced throughout the whole extent of the air-passages, is the most prominent symptom. It is combined with a more or less frequent and labored respiration, interrupted by violent fits of coughing.

In consequence of the increased secretion from the mucous glands, caused by the severe irritation, the trachea and bronchial tubes are soon filled with secretion, which is often mixed with blood, and is expelled in large quantities during the paroxysms of coughing. The moist râles produced by it are easily distinguished by auscultation.

The vocal cords, as a rule, cease to perform their work. Either complete aphonia occurs, or speaking aloud, when at all possible, causes severe pain and coughing.

All these phenomena increase in intensity during the first few days after the poisoning. In consequence of the increasing swelling of the mucous membranes, and the gradual development of denser masses of exudation and ulcers, the lumen of the air-passages becomes more and more reduced, and the breathing becomes more labored. The frequency of respiration increases at the same time. A painful feeling of suffocation, accompanied by violent pains in the region of the larynx and under the sternum, deprives the patient of sleep. Even after slight poisoning by ammonia fumes, a severe catarrh of the air-passages is left,

which persists for a long time. The lungs themselves, as it appears, are not, as a rule, involved in the inflammation. In only a very few cases have the vestiges of a pneumonia been found at the autopsy. As might be expected, however, whenever the above-described phenomena persist for a long time, they may readily prove fatal through the agency of œdema of the lungs.

Scarcely less intense are the local symptoms of reaction, when considerable quantities of caustic ammonia are taken into the mouth and stomach. The most violent pains are experienced wherever the poison comes in contact with the mucous membrane, which is richly supplied with nerves; they are especially severe in the pharynx and throughout the length of the œsophagus, where they are usually felt immediately after the poison is taken, while the pain in the epigastrium, which is very constantly present, appears later. Great difficulty in swallowing and violent vomiting follow quickly upon the ingestion of the poison.

On the organs of the mouth the poison leaves visible traces of its action. The lips swell greatly, as do also the tongue and the soft palate, the last assuming at the same time a bright scarlet hue; small extravasations of blood may also be found upon them. In two cases profuse salivation[1] was observed. The matter ejected during the frequent attacks of vomiting contains more or less blood, and much tough mucus. The fæces and urine are sometimes retained at first, but later on abundant discharges occur, which at times are passed involuntarily. In several cases the patients were exhausted by very obstinate, profuse, bloody diarrhœas. The epigastric pain is scarcely ever wanting, and the abdomen is very sensitive to pressure. The administration of nourishment is attended with great difficulty, on account of the extreme dysphagia.

The pulse usually becomes very rapid (140), and is at the same time small and weak. The temperature of the body appears to be reduced, the extremities are cold, and the patients invariably complain of feeling cold. In a very few of the cases fever set in at a later stage.

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[1] Case of *Fonssagrives*, by Tardieu, loc. cit.

In general the patient presents the picture of profound collapse: the face is pale, the eyeballs are sunken and surrounded by dark rings, and the visible mucous membranes are livid or cyanotic.

The sensorium is, as a rule, unaffected, and the patient is fully conscious of the agony he is suffering.

At a later stage somnolence and sopor supervene; convulsions and other nervous symptoms have been but seldom observed, and then only in cases where camphor had been administered in addition to the ammonia.

Wandering neuralgic pains in the muscles, formication, and complete anæsthesia, ringing in the ears and dizziness, are symptoms of which mention has been made only in a few cases, among which the only case of poisoning by sal ammoniac,[1] which can be found in the literature, is included. In the case of the two-year-old child already mentioned, the injection of ammonia into a nævus immediately caused violent general convulsions and death.

The case reported by Potain,[2] in which a diffused erysipelas accompanied the ammonia poisoning, is also unique. The course and termination of poisoning by ammonia compounds are of course determined by the quantity of the poison used, and the therapeutic means resorted to. On the whole, the course is comparatively slow, the symptoms lasting for several days or even weeks. Death is due either to the disturbances of respiration, or to the weakness resulting from the affection of the digestive organs. In mild cases the recovery is rapid and complete, and is not followed by any serious sequelæ.

The pathologico-anatomical lesions of this form of intoxication, like those of many others, present nothing that is characteristic, unless, indeed, we attribute importance to the isolated observation of croup-like pseudo-membranes in the larynx and trachea of one patient. Ordinarily we find in the respiratory organs only the signs of a more or less intense, simple inflammation—namely, swelling, loss of epithelium, redness, and sometimes scattered superficial ulcers. The œsophagus and stomach

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[1] *Crichton-Brown*, Lancet. 1868.

[2] L'Union méd. 1857.

are similarly affected; the visible local destructions caused by the ammonia scarcely ever extend beyond the stomach. A purely symptomatic treatment is the best to pursue. When caustic ammonia has been taken, and the case is seen immediately, the administration of diluted acids is indicated theoretically, and has frequently been put in practice. As a rule, ordinary vinegar, which is to be found in every house, is used, or sometimes lemon juice; both should be given in a very diluted form. At a later stage, this antidotal treatment is of course useless. Moreover, the dysphagia of the patient always presents an obstacle to its employment.

To the use of the stomach-pump there is no special objection, but emetics must be avoided. The French authors have repeatedly used local blood-letting, such as leeches on the neck and epigastrium, according to their own accounts, with good results. When the dyspnœa is very severe the question of tracheotomy will of course present itself.

The treatment of the other symptoms does not require an extended consideration; it must be regulated according to the general laws.

CHAPTER II.

POISONING BY CAUSTIC AND CARBONATED ALKALIES (POTASSIUM AND SODIUM).

Although the difference in the constitutional action of potassium and sodium salts has in recent times been very positively demonstrated, we can still treat of them both together when their local caustic effects come into question; for in this respect no difference can be detected in their action.

The poisoning in question here closely resembles in its nature that produced by the concentrated acids. At most it presents a few noticeable modifications as regards the intensity of the phenomena and the course.

The caustic alkalies also, the chemical properties of which we assume to be known, are chiefly dangerous to the animal tissues

on account of their affinity for water. To a less degree, their behavior towards the free acids in the tissues and the acids combined with weaker bases, as well as towards the albuminous substances, comes into question; all three are deprived of their functions in the organism by an excess of these alkalies. Upon these chemical reactions, which take place immediately at the point of contact, depends their caustic action.

On the sensory nerves contained in cauterized spots they act as violent irritants, and thus provoke intense pain; the parts surrounding these spots react by developing inflammation. The high diffusive power of the alkalies in solution is exceptionally favorable to the extension of their caustic action into the deeper layers of the tissues. The acids, when in a concentrated form, convert the tissues into discolored, dark, tinder-like masses, but the caustic action of alkalies produces less discolored, greasy masses resembling salve. When the alkali meets with tissues containing much fat, a soap is formed.

The action of the carbonates of the alkalies is very similar to that of the caustic; the carbonic acid, being but feebly combined, is easily displaced when they come in contact with the secretions of the stomach.

The toxicological importance of the substances here discussed is not very great. Cases of poisoning by them, as a rule, owe their existence to accident. Being much used in manufactures, they are readily accessible to every one. Cases of poisoning occur not only from potash and soda lye, but sometimes also from soap-water, which always contains free alkali. Several cases of this sort have resulted from the substances designated being mistaken for purgatives. Tardieu[1] also reckons the eau de javelle, which is a solution of sodium hypochlorite,[2] among those substances which act in the same way as the free alkalies, and mentions cases which afforded the characteristic phenomena of poisoning by lyes. Here, however, a part of the action should properly be ascribed to the chlorine. Casper[3] reports a case of attempted murder by soda lye, and Tardieu describes two cases

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[1] Loc. cit. p. 234.

[2] See previous note (p. 288).

[3] Loc. cit. II. p. 495.

where potash lye and potassic carbonate respectively served for suicidal purposes.

In the literature we could find in all only eighteen cases of this form of poisoning. Of these five were caused by potash,[1] two by soda lye,[2] seven by potassic carbonate,[3] one by soap-water, and three by eau de javelle.[4] Fifteen cases terminated fatally, and only three in recovery.

With respect to the toxic and fatal dose, no satisfactory conclusion can be deduced from the material at our command. Tardieu (loc. cit.) holds that from two and a half to five drachms of sodium or potassium hydrate is sufficient to cause death. The fatal cases that are reported in the literature of the subject are of little value in this connection, because in almost all of them the concentration of the solutions used is unknown.

The symptoms of poisoning by lyes differ from those caused by acids only in intensity.

The repulsive taste of the liquids, and the severe pain that is experienced immediately when they are very concentrated, as a rule cause the poison to be spat out at once, so that in all cases only a comparatively small quantity reaches the stomach. This organ instantly reacts by violent vomiting. Loss of consciousness and convulsions, symptoms of reaction on the part of the nervous system, which are so frequently observed in sulphoxysm, occur only exceptionally in poisoning by lyes.[5]

On the other hand, the pains in the pharynx, œsophagus, stomach, and epigastric region are not much less severe than in the case of poisoning by acids. Loss of the power of speech and extreme dysphagia are also seldom absent.

The visible portions of the mucous membrane of the mouth and throat are more or less altered; sometimes they merely assume a bright-red color, but again they are covered with a brownish film, and are entirely denuded of epithelium in spots.

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[1] *Deutsch* (Preuss. Ver.-Ztg. 1857), *Boudet*, *Behier* (Tardieu, loc. cit.), *Dewar*, *Pallas* (Frank's Magaz. III.).

[2] *Casper* (loc. cit.), *Leischmann* (Jahresber. v. Virchow und Hirsch. 1867).

[3] *Dewar* (loc. cit.), *Liègard* (Frank's Magaz.), *Orfila* (loc. cit.), *Barclay* (Taylor, loc. cit.), *Tardieu* (loc. cit.), *Espagne* (Arch. gén. 1867).

[4] *Tardieu*, loc. cit.

[5] *Liègard*, loc. cit.

The vomit has at times a greasy, salve-like consistency, and is seldom bloody; its alkaline reaction has been frequently demonstrated; in very severe cases shreds of necrotic mucous membrane are thrown up. Intestinal symptoms are, as a rule, wanting.

The constitutional symptoms are similar to those of a moderately severe case of acid poisoning, and require no detailed account.

We will speak later of the specific action of potassium; in poisoning by lyes it scarcely ever manifests itself in an unequivocal manner.

The patients usually recover from the immediate effects of the poison when this consists of lye, but very frequently a chronic affection is left behind, which may prove fatal months afterwards. In ten of the above-mentioned eighteen cases strictures of the œsophagus were developed, which led to inanition. The chronic inflammation which causes these cicatricial strictures is usually located in the lower third of the œsophagus. In one case a large abscess formed, which discharged into the œsophagus, and opened a communication between it and the right pleural[1] sac.

It is not necessary to describe in extenso the symptoms caused by these secondary disorders. A simultaneous affection of the lungs (pneumonia) was observed in Casper's case; it evidently resulted from the local irritation produced by the penetration of some of the poison into the air-passages.

The pathologico-anatomical examination demonstrated, without exception, the limitation of the lesions to the mouth, pharynx, œsophagus, and stomach; they never extended into the intestines.

Even in the stomach we find, as a rule, only a few small ulcers, or their residua. In cases which had run a chronic course we find, in addition to the cicatricial strictures, all the signs of inanition—namely, emaciation, anæmia, atrophy of the gastric walls and of the muscular coats of the intestines, etc.

In the treatment of poisoning by lyes, the indicatio causalis

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[1] *Leischmann*, loc. cit.

is fulfilled by removing any of the poison remaining in the stomach by means of the stomach-pump. Besides this, a liberal administration of acid drinks (vinegar, lemonade, and the like) is to be recommended; otherwise the management of the case must be purely symptomatic.

A judicious treatment of the cicatricial strictures with bougies, together with careful feeding, has brought about a favorable result in several chronic cases.

Caustic lime plays a still more subordinate rôle in toxicology than the alkalies. The disorders which are produced by its external action must, of course, remain unconsidered here.

Quick as well as slaked lime acts in a similar manner to the other alkalies, and when introduced in large quantities into the stomach may provoke gastro-intestinal symptoms.

In the literature but three cases[1] of poisoning by this substance are recorded. They present no points of special interest.

The poisonous qualities of the soluble lime salts (calcium chloride), which were determined by Blake[2] and others, by experiments on animals, have been verified by researches instituted by Mickwitz and the author.

CHAPTER III.

POISONING BY SALTS OF THE ALKALIES AND EARTHS (ESPECIALLY POTASSIUM NITRATE).

All the salts of the alkalies and earths that are soluble[3] in water, when introduced into the system in considerable quantities, provoke disturbances which vary according to the diffusive power of each combination, and hence must, in a certain sense, be regarded as local effects. The nature of the base has no influence in the production of these effects. For instance, the salts

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[1] *Timaeus* (Christison, loc. cit.), *Gmelin* (Gesch. d. Mineralgifte), *Lion* (Frank's Mag. I. p. 209).

[2] Loc. cit., Edinb. Med. Journ. 1841.

[3] We except, of course, those salts which exert a specific poisonous power, by virtue of their acid (potassium cyanide, alkaline arsenites and arsenates, etc.). These will be treated of under the heads of the poisons which they contain. The alkaline sulphides also must be considered under sulphuretted hydrogen, and the hypochlorites under chlorine.

which are only slightly diffusible provoke diarrhœa, while those which are readily diffusible cause diuresis. When administered in large quantities in the solid form or in highly concentrated solutions they all act as caustics by the abstraction of water, and produce gastro-enteritis.

Apart from these local effects the bases of certain of these salts possess more or less decided specific poisonous qualities. Of the more common of these bases sodium is the only one that has so far proved to be absolutely innocuous. The poisonous nature of potassium has recently been absolutely demonstrated, while that of barium has long been known. Lime and magnesia, although up to the present time they have had no toxicological importance, must, in accordance with the results of experiments, also be classed as poisonous, while strontium, like sodium, is innocuous.

On the whole, however, the specific poisonous quality of these substances manifests itself unmistakably only when they are introduced directly into the blood in large quantities. Such quantities as are absorbed from the intestines, as a rule, do not suffice to produce these so-called constitutional effects. Of all these substances barium—which will be considered at length in another place—is unquestionably the most poisonous. The potassium compounds come next, while lime, magnesia, and strontia probably never produce constitutional effects when absorbed from the stomach.

We shall confine ourselves here to the discussion of poisoning by potassium nitrate. While speaking of it in particular, however, the opportunity presents itself to indicate the local effects which are common to most of the salts, apart from the specific action of the potassium.

Although even the older observers noticed a difference in the action of sodium nitrate and potassium nitrate, and although Blake in his experiments—to which hitherto very little attention has been paid—attained results which proved potassium to be exceedingly poisonous, this fact, nevertheless, was not generally admitted until the year 1864. It was chiefly the experiments of Grandean [1]

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[1] Journ. de l'anat. et phys. 1864.

and Traube[1] which led to its universal acceptance; and by a natural reaction its importance soon became greatly overestimated.

In respect to their absorption and elimination, and their chemical behavior while in the blood, the potassium salts differ in no respect, as far as can be determined, from the other soluble salts. The certainly striking brightness of the arterial blood, which is invariably observed in animals poisoned by potassium salts, cannot as yet be utilized in any way. The knotty point about potassium poisoning consists rather in the numerous remarkable and absolutely inexplicable effects which the substance produces upon the functions of the heart and the nervous system, in spite of its being itself an integral constituent of the body.

The potassium salts, when introduced in considerable quantities directly into the blood of either cold-blooded or warm-blooded animals, stop the movements of the heart.[2] Cold-blooded animals are, before this occurs, deprived of the power of voluntary motion, while warm-blooded animals, after the cessation of the heart's action, die in more or less developed convulsions. Traube (loc. cit.) compared the action of potassium on the heart to that of digitalin, and emphasized particularly the analogous influence of both substances on the blood-pressure. However, this correspondence in the action of potassium and digitalin can hardly be proved satisfactorily. Bunge's[3] experiments on cats and dogs did not confirm Traube's statements cencerning the blood-pressure. Moreover, Mickwitz[4] and the writer have never seen the blood-pressure increase after poisoning by potassium in animals which had not been curarized; on the other hand, an increase in the pressure invariably ensued after previous poisoning by curari.

The study of the behavior of the cardiac nerves in mammals has contributed just as little towards explaining the nature of the paralyzing action of potassium on the heart as have the ex-

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[1] Ges. Abhandlung. I.

[2] *Guttmann*, Berl. klin. Wochenschr. 1865. Virch. Arch. XXXV. *Podcopaew*, Virch. Arch. XXXIII.

[3] Pflueger's Arch.

[4] Inaug.-Dissert. Dorpat. 1874.

periments on frogs. Still the investigations[1] which the writer instituted in connection with Mickwitz have opened up to him some new points of view. He found that the paralysis of the heart produced in mammals by the potassium salts is only apparent, and that by patient persistence in artificial respiration, and by mechanical irritation of the heart (compression of the thorax) the action of the heart can be entirely restored.

Since animals which had already lain for thirty-eight minutes apparently dead, and entirely without pulsation in the heart, were completely restored to life by these means, it is evident that the potassium cannot possibly occasion a profound alteration in the physiological condition of the heart. It is more probable that the effects produced by it are due to temporary anomalies of excitability in the automatic central organ of the heart. After the awakening of the heart from its apparent death, it shows a striking increase of energy in comparison with its action before the poisoning ; this manifests itself both in the frequency of the pulse and in the blood-pressure. These striking facts are not altogether without parallel, since a frog's heart, when its pulsations have been stopped by the action of potassium, can again be set in operation by mechanical irritation, and its contractions are then remarkably energetic.

The effects produced by potassium on the rest of the nervous system consist in a transitory stage of excitement, which is followed by general paralysis ; more or less general clonic spasms precede the paralysis both of the motor and the sensory centres. Respiration does not cease until after the heart's action stops.

After awaking from the apparent death, the respiratory muscles do not regain their power of spontaneous movement until some time after the heart has resumed its action ; the animal is still in a state of total narcosis, and does not respond to irritations of any kind. After the lapse of considerable time the reflex actions gradually return, and then an abnormal increase in the reflex excitability is frequently observed. This increase in the reflex excitability may be so great, that even trifling causes (a

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[1] Compare Centralbl. f. d. med. Wissensch. 1874. Ueber Wiederbelebung nach Vergiftungen.

shaking, a gentle touch on the surface of the skin) may cause spasms. The local effects produced by the potassium salts on the stomach and intestinal canal are essentially similar to those produced by all other analogous combinations; they consist in a gastro-enteritis, which varies in violence according to the size of the dose.

Cases of poisoning by potassium nitrate are not very frequent. In the majority of cases they arise from mistaking this poisonous salt for the common purgative salts (Glauber's and Epsom salts).

The following small table gives the most important points of all the cases that are to be found in the literature:

No.	Sex and Age of Individual.		Quantity of Poison.	Result of the Poisoning.	Cause.	Observer.
1	Man	50	℥ i.	Recovery.	Mistake.	Oberstädt.
2	Man	30	ʒ VI.	Recovery.	Mistake.	Deutsch.
3	Man	?	℥ III.	Death in 5 hours	?	Jour. d. Chimie
4	Man	20	℥ i.	Death.	Mistake.	Mouton.
5	Girl	?	℥ i.	Recovery.	Mistake.	Rust's Magaz.
6	Woman	48	℥ i.	Death.	Mistake.	Laflize.
7	Woman	36	℥ i.	Death.	?	Jouville.
8	Woman	?	℥ ii.	Recovery.	Mistake.	Buttler.
9	Woman	24	℥ ii.	Recovery.	Mistake.	?
10	Man	40	ʒ ii.	Death.	Clyster.	O. A. Meyer.
11	Man	?	℥ ss.	Recovery.	?	Ritter.
12	?		ʒ vjss.	Death.	Mistake.	Chevallier.
13	Woman (pregnant)	?	A handful.	Recovery. (Abortion.)	Mistake.	Alexander.

The figures here given demonstrate the impossibility of determining with accuracy the fatal dose for human beings.

The symptoms of poisoning by nitre begin usually with violent purging and vomiting, combined with severe pains in the epigastric region and the abdomen. In rare cases the masses ejected by vomiting are bloody. To these phenomena coldness of the extremities, cold sweat, and sometimes also painful strangury and tenesmus are very soon added. The pulse is frequent, small, and irregular; the respiration sometimes labored.

The constitutional phenomena which are due to the action of potassium were unequivocally present in five of the above-mentioned thirteen cases. They consisted in a feeling of intense

anxiety, pains in the back, spasmodic contraction of certain muscles (pectorals, calves of the legs), aphonia, general convulsions, loss of consciousness, and coma. In Mouton's case, the local phenomena were said to have been entirely absent. Death ensued in from five to sixty hours.

Among the symptoms which occur only in special cases, we may mention abortion, which was observed in Alexander's case; also peculiar choreic movements, which, in another case observed by Buttler, that of a pregnant woman, are said to have continued for two months after the poisoning.

Sometimes recovery takes place very gradually, various nervous symptoms (twitchings, neuralgic pains, etc.), as well as disorders of digestion, persisting for a long time as secondary effects.

The pathological appearances at the autopsy are limited to the frequently described lesions of gastro-enteritis.

The treatment is purely symptomatic. When the patient is asphyxiated or comatose, we must, in accordance with the knowledge gained from experiments on animals, recommend the energetic employment of artificial respiration, with compression of the thorax in the region of the heart.

CHAPTER IV.

POISONING BY BARIUM COMPOUNDS.

As regards poisonous qualities, the barium compounds hold unquestionably the first place among the salts of the alkalies and earths. Nevertheless, they are only of subordinate importance in practical toxicology, because cases of poisoning by them are of exceedingly rare occurrence.

Barium carbonate and chloride are the only preparations which must be considered in this connection, and the chloride (terra ponderosa salita), in consequence of its solubility in water, is absorbed without any further change, and acts as a poison, not only when taken into the stomach, but also when injected into the subcutaneous cellular tissue or into wounds; the carbonate, on the other hand (baryta carbonica, witherite), being but little

soluble in water, is only poisonous in so far as it can be transformed into soluble combinations (barium chloride) in the digestive fluids.

Experiments on animals by different authors have, moreover, proved that all the other soluble barium salts possess a like poisonous power.

The passage of the barium combinations into the urine has been regarded as proved by the observations of Krahmer and Orfila;[1] no recent investigations of this point have been reported.

Barium is reckoned among the poisons which exert a local irritating as well as a constitutional action; evidently only because among the symptoms of acute barium poisoning vomiting and diarrhœa are seldom wanting. Since, however, the anatomical lesions characteristic of local irritation are usually absent, and since the symptoms ascribed to it are also, as it appears, observed after the direct introduction of the poison into the blood, we see no grounds for endorsing the assumption that barium exerts a local irritating action. Very large quantities of the substance will of course produce the local effects which are common to all salts. Concerning the real cause of the poisonousness of the barium compounds we are absolutely ignorant. The surmise of Onsum,[2] that the poison is converted in the blood into an insoluble sulphate, which in a purely mechanical manner produces emboli in the lungs, has been confuted by Cyon.[3]

Judging from the symptoms, the action of barium must be compared to that of the narcotic poisons.

The experiments made upon animals prove that the poison exerts an undoubted influence on the circulatory apparatus. Even the older toxicologists called barium a heart poison,[4] and Cyon (loc. cit.) has recently demonstrated this property of the poison by experiments on frogs and rabbits.

In mammals the cessation of the heart's action after the administration of barium has been observed by numerous

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[1] See *Husemann*, Toxikologie.

[2] Virch. Arch. Vol. XXXVIII.

[3] Arch. f. Anat. u. Physiolog. 1866.

[4] *Orfila* (loc. cit.), *Brodie*, *Blake*, and others.

authors; some have even emphasized the lack of excitability shown by the paralyzed heart when irritants are applied to it.

The investigations recently undertaken by Mickwitz,[1] under the direction of the writer, have defined somewhat more precisely the nature of this cardiac paralysis. Although it is not possible to determine from them whether this paralysis is confined solely to the cardiac nerves, or affects also the muscles of the organ, still, the cessation of the heart's action during *systole* has been shown to be a constant phenomenon both in warm and cold-blooded animals: in mammals (cats) especially, the cartilaginous consistency of the left ventricle is striking. In this connection the parity of action between barium and digitalis can hardly be overlooked. The blood-pressure increases enormously after the injection of small quantities of barium solutions into the veins, but the increase is, as a rule, preceded by a not inconsiderable lowering of the pressure. The increase often occurs very suddenly, and the pressure not infrequently becomes three or four times as great as before; at the same time the pulse becomes much more rapid. Increasing the dose then causes a steep sinking of the pressure-curve, and paralysis of the heart. Division of the spinal cord in the neck does not at all interfere with the development of this phenomena, and hence it does not appear improbable that the muscular coats of the vessels, as well as the heart, are affected by the poison. This hypothesis receives support also from the state of excessive contraction into which, as our own investigations show, the smooth muscular fibres of the intestine and bladder are thrown by the poison. Both organs lose their lumina completely in cases of barium poisoning. This peculiarity, which has not hitherto been noticed by any other writer, and which can be recognized even during life by the exceedingly active peristaltic movements of the intestines that are visible through the abdominal walls, seems to us to afford also a sufficient explanation of the alleged gastro-intestinal symptoms (diarrhœa and vomiting). It indicates a certain preference of barium for the tissues composed of non-striated

[1] Inaug. Diss. Dorpat. 1874.

muscular fibres, or for the nerves contained in them, which is characteristic of the action of the poison.

In cold-blooded animals the other symptoms, caused by the action of the poison on the nervous system, consist in paralysis of the voluntary muscles, which is, however, preceded by a peculiar state of rudimentary, clonic spasms.[1]

Frequent tetanic spasms are seldom absent in mammals. The disturbances of the respiration are evidently dependent upon the anomalies of the circulation which precede them.

Since in all the literature of toxicology, both old and recent, only very few cases of poisoning by barium compounds can be found, it may be assumed that this form of poisoning belongs to the rarities. In the few cases that have been reported the poisoning was due to inappropriate medicinal use of barium chloride, or to the chloride or some other barium salt having been mistaken for Epsom salts,[2] Glauber's salts,[3] sublimed sulphur,[4] or Carlsbad salts.[5] Once a powder for rats, consisting of barium chloride, was taken with suicidal intent; finally, one case has been reported where temporary symptoms of poisoning occurred in a child who had chewed a paper collar, in the coloring of which heavy spar had been used. The use of barium nitrate in pyrotechnics for the production of the so-called green fire might also cause poisoning, while the sulphate, which is used as a pigment on account of its insolubility, is almost innocuous.

As for the toxic and fatal dose, no satisfactory figures can be given on account of the meagreness of the material at our command. One drachm of the carbonate and half an ounce of the chloride have proved fatal to adults. However, these are not by any means the smallest quantities that may prove fatal.

The clinical phenomena are composed of varying nervous and gastro-intestinal symptoms. Nausea, anxiety, and vomiting usually open the scene; these are followed by epigastric pains, pro-

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[1] Compare on this point the essay of the writer on Barium Salts. Arch. f. exper. Path. u. Pharm. 1875. III.

[2] *Wolf*, Casper's Wochenschr.

[3] *Wach*, Henke's Zeitschr. für Staats-Arzneikunde. 1835.

[4] *Tidy*, Med. Press and Circ., Jahresber. v. Virch. u. Hirsch. 1868. p. 325. I.

[5] Virchow u. Hirsch, Jahresber. 1867. p. 443. I.

fuse diarrhœa, and severe colicky pains, which themselves usher in the nervous symptoms; ringing in the ears, diplopia, præcordial anguish, weakness of the muscles, eccentric pains, cramps in the calves of the legs, and general convulsions. Loss of sensibility and paraplegic phenomena have been observed in two cases.

Among the more constant phenomena we must mention coldness and paleness of the skin. In one case mention was made of a full, hard pulse. The course of the poisoning was several times very rapidly fatal.

Characteristic pathologico-anatomical lesions are lacking; twice the signs of a gastro-enteritis toxica were observed, and once even perforation of the stomach was found.

The treatment must be primarily directed to the removal of any of the poison that yet remains in the stomach. For this purpose the stomach-pump is the best means at our disposal. Emetics (apomorphia) may also be used.

As chemical antidotes magnesium and sodium sulphates are recommended; they should be administered in large quantities of water. Otherwise the treatment must be purely symptomatic. The paralysis of the heart can sometimes, as is evident from our experiments on animals, be overcome by persistent irritation of the heart (forcible compression of the thorax and artificial respiration) continued for several minutes. In desperate cases in men this mode of treatment, or even acupuncture of the heart, should not be left untried.

CHAPTER V.

POISON BY ALUM (ALUMEN).

Alum, which is so extensively used in manufactures, the arts, and medicine, must, according to both ancient and modern experience, be classed among the more powerful poisons. A double combination of potassium sulphate with aluminic sulphate produces this salt, which is a colorless, crystalline, strongly acid substance; it is readily soluble in water, and has a strong astringent taste.

Mitscherlich has studied the action of alum upon albuminous substances, and has found that their solutions were precipitated by solutions of alum. The precipitate contains both alum and albumen, and hence, according to the current terminology, it is designated as alum-albuminate. The passage of alum from the stomach into various secretions has been frequently demonstrated.

The experiments hitherto made with alum have been undertaken solely with a view to determine the answer to the question whether it is really poisonous. Christison (loc. cit.) considers it almost absolutely harmless, and Orfila also (loc. cit.), on the occasion of a medico-legal investigation of a case in Paris, ascribed to it only a very trifling poisonous action. Although the experiments made, some of them by Orfila himself, have established the poisonous power of alum beyond question, nothing has been learned from them regarding the nature of its toxic action. Whether the active agent is free sulphuric acid, as Tardieu[1] thinks, or the potassium salt, or, finally, the alum as a whole and as a poison sui generis, cannot as yet be decided.

The reaction of alum with albumen furnishes a simple explanation of the corrosive action of the salt in the solid form or in concentrated solution. The emetic action of the poison also, which we have learned both from Barthez's[2] experiments on himself and from the cases of poisoning that have been observed, might possibly be regarded as the consequence of a local affection of the mucous membrane of the stomach. The great rapidity with which a case, recently observed by Ricquet,[3] proved fatal, and some symptoms noted in previous cases of poisoning (tremor of the muscles, spasms, depression, etc.) give us reason to suspect that alum exerts also a constitutional action, the more so as in Ricquet's case the local lesions caused by the poison were found at the autopsy to be comparatively slight, and entirely out of proportion to the rapidly fatal course of the poisoning.

Tardieu (loc. cit.) speaks of a woman who wilfully murdered

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[1] Toxikologie. II. edit. 1875. [2] Frank's Magaz. III.

[3] Journ. de Pharm. et de Chim. Oct. 1873.

her three-months-old child by administering to it about 0.9 gramme (fourteen grains) of alum. In the majority of the other cases of acute poisoning the alum was taken by mistake for other medicinal preparations (*e. g.*, magnesic sulphate, Ricquet). Von Hasselt states that cases of poisoning also arise sometimes from the administration of too large doses of alum by order of the physician. The sophistication of flour with small quantities of alum, which is much practised in England, appears to have no toxicological importance, although Snow[1] finds in it one cause of the prevalence of rhachitis.

To the three cases of alum poisoning described by Von Hasselt, Taylor, and Husemann, we must add one case reported by Ricquet, and two cases by Tardieu (loc. cit.), all of which terminated fatally.

In the mentioned case of Tardieu, 0.9 gramme (fourteen grains), in that of Ricquet, 30 grammes (nearly one ounce) of alum were administered.

Of all the symptoms the most constant are the pains in the cavity of the mouth, in the œsophagus and stomach, which are experienced immediately after taking the poison, and also the vomiting, which comes on very soon and is sometimes bloody. Ricquet also observed severe dysphagia, torturing thirst, and retention of fæces. Several writers mention great weakness of the muscles and depression. The consciousness is unclouded. There is great anxiety and sometimes a convulsive tremor of the muscles is observed. The pulse is exceedingly small and frequent. After repeated fainting-fits and after a considerable reduction of temperature below the normal point, death ensued inside of twenty-four hours.

At the autopsy, yellowish-gray deposits were found on the mucous membranes of the mouth, pharynx, and œsophagus; the tongue and palate were swollen. The stomach, intestines, and kidneys were hyperæmic, but without noticeable loss of substance. The chemical tests for the poison were repeatedly employed successfully.

No special rules for treatment can at present be laid down.

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[1] *Husemann*, Toxikol.

SECOND PART.

Poisoning by Anæsthetics and other Poisonous Carbon-Compounds.

FIRST DIVISION.

Poisoning by Anæsthetics.

CHAPTER I.

POISONING BY ALCOHOL—ACUTE AND CHRONIC ALCOHOLISM.

Ethyl-alcohol ($\text{Є}_2\text{H}_5\Theta\text{H}$), as a constituent of various fermented liquors (beer, wine, etc.), and spirits (brandy, rum, arrack, cognac, etc.), is one of the most widely diffused luxuries of civilized nations. Its useful or pleasant qualities do not now concern us. In these pages we only notice it so far as it proves injurious to health. The different kinds of alcoholic liquors are for the most part important in proportion to the quantity of alcohol they severally contain. It is only in a very few cases that the differences in their other qualities are of any importance. If we take any notice of their quality, it is generally because some other injurious ingredient accompanies the spirit of wine. To this category some not very important ethers, and *absinthe*, largely used in France, belong. Alcoholic liquors are often purposely adulterated, but these adulterations do not now concern us.

Alcohol, free from water (anhydrous alcohol), is lighter than water, but freely miscible with it in all proportions; it forms a colorless, volatile liquid, which burns with a blue flame. The vapor has a characteristic and agreeable odor, and alcoholic solu-

tions have a pleasant taste, which is combined with an intense feeling of burning.

Concentrated spirits of wine, or alcohol with but little admixture of water, acts upon animal tissues just like irritant corrosive poisons. This is very likely due to its strong affinity for water—the less water it contains, the more eagerly will it attract water to itself. For the most part, however, in alcoholic poisoning, the local injuries are unimportant when compared with the general symptoms which spring from the absorption and reception of the poison into the circulation—in other words, into the blood. Absorption may take place in several ways. Although not strictly proven, it seems highly probable (considering the remarkable power of diffusion possessed by alcohol) that it can be absorbed into the blood by absorption through the unbroken skin. Alcohol, in the form of vapor, is diffused into the blood from the internal surface of the lungs. It goes through the tissues of the mucous membranes, straight into the blood-vessels, mixed with water. Bouchardat and Sandras[1] state that spirits of wine introduced into the stomach is almost all absorbed by the gastric veins (though the intestinal veins absorb some), whilst none of it will be taken up by the lymphatics and lacteals. Lastly, alcohol may be absorbed by the surface of suppurating wounds; indeed it is not very uncommon to note a good deal of drunkenness after the application of spirit lotions[2] or spirits of camphor to the stump of an amputated limb.

Alcohol is eliminated from the body by three channels: the air expired from the lungs, the urine, and the skin. Although it had long been suspected from the smell of the breath that alcohol was eliminated by the lungs, this has of late years been determined experimentally by Lallemand, Perrin and Duroy,[3] and by Parkes and Wollowicz,[4] who have proved by indisputable chemical tests that alcohol can be detected in the air breathed out from the lungs of healthy men who have taken

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[1] Annal. de Physique et Chimie. 1847.

[2] See *Chédevergne*, Bullet. gen. de thérap. LXVII., and *Peronne*, De l'alcoolisme dans ses rapports avec le traumatisme. Paris. 1870.

[3] Du rôle de l'alcool et des anæsthésiques, etc. Paris. 1860.

[4] Proceed. of the Royal Soc. Vol. XVIII. p. 362.

alcohol. The same experimenters discovered alcohol in the secretions of the skin. It has also been recovered from the urine by distillation, not only by Lallemand, Perrin and Duroy, but also by Baudot[1] and Schulinus,[2] although only in small quantities.

It is by no means equally clear how the alcohol that is retained in the system is disposed of; in other words, what becomes of the alcohol not eliminated as such is not so easily settled. The hypothesis propounded by Liebig,[3] and at one time generally accepted, that alcohol in the blood and in the tissues undergoes combustion, and is converted into carbonic acid and water, and by its mere presence hinders the combustion of other materials of far greater importance in the organism (lessens tissue-changes), has not been confirmed by experiments any more than the assertion of Duchek[4] that aldehyd and oxalic and acetic acids are formed in the body out of alcohol. Both Masing,[5] who worked under the supervision of Buchheim, and Lallemand, Perrin and Duroy sought in vain to discover these bodies in the blood after alcohol had been introduced into the stomach. These authors conclude from this, and from the fact that undecomposed alcohol can be detected in the blood and in most of the organs of the body, that alcohol passes through the system without undergoing any changes or decomposition. The French authors even go a step farther, and maintain, on the basis of quantitative determinations, that alcohol may be retained, and even accumulated, in certain organs, such as the liver and the brain, by reason of a sort of affinity for these organs, and retained a long time. It would seem, however, from the researches of Schulinus [as well as from those of Dupré and Anstie —TRANS.], that this opinion is based upon errors inseparable from the mode of analysis employed by the French experimenters.

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[1] L'Union Méd. 1863.

[2] Inaug. Dissert. Dorpat. 1865.

[3] Thierchemie. III. Aufl. S. 59. *Böcker* (Beiträge zur Heilkunde. I. S. 258) was one of the very first to combat this view energetically, and has shown in himself that the excretion of carbon dioxide is considerably lessened by the ingestion of alcoholic drinks.

[4] Prager Vierteljahrschrift. 1853.

[5] Inaug.-Dissert. Dorpat. 1854.

Schulinus differs from Lallemand, Perrin and Duroy, in so far as he feels compelled to admit that there is a partial destruction or decomposition of alcohol in the blood; because, if we kill an animal soon after its ingestion of alcohol, only a fractional part of that alcohol can be recovered, either from its excretions or from the blood itself, or from the organs of the animal. What kind of decomposition goes on, he could not, however, determine; and this question still remains undecided. As regards the behavior of alcohol in relation to the various constituents of living organisms, our first thoughts, almost of necessity, turn to its power of coagulating albuminous solutions. But though strong alcohol is one of the most certain means of precipitating the majority of albuminous substances, yet we may pretty safely assert that its physiological action, and, indeed, its action when introduced in moderate quantities into the blood itself, is not that of coagulation. Alcohol produces precipitates in gastric juice, and in solutions of peptone. In a living frog one can clearly see a dark coloration of the circulating blood soon after the introduction of two cubic centimetres (about ʒ ss.) of alcohol into one of the lymphatic hearts, or into the cavity of the peritoneum. But in mammalia and in human beings no change recognizable by our present methods of observation is brought about by the introduction of alcohol. Bonwetsch[1] states that, in ox-blood diluted with water, the reduction of the oxyhæmoglobin by stannous oxide soda solution occurs more slowly after the addition of alcohol than it does when no alcohol is present. This fact seems to show that the poison has some affinity for oxyhæmoglobin. The alcohol which circulates with the blood modifies the normal course of organic functions in various ways. The outward symptoms or phenomena, which are the expression of these disturbances, are like those induced by other narcotics. The nerve-centres, to which the poison has access, have their functions stimulated and increased at first, and then their activity is gradually more or less perfectly abolished for the time. These effects are much modified by the different quantities of the poison taken, and by the time during which the poison

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[1] Inaug.-Dissert. Dorpat. 1869.

works, so that we get a variety of phenomena, in which sometimes only the stage of excitement, sometimes only the paralytic stage, or both successively, in singular combinations, are presented to us. The extent to which alcohol affects the nervous system is by no means restricted. Its domain is a wide one. If the results are at first limited to the cortical portion of the brain in the first instance, they may gradually extend so as to embrace almost all the central organs; the centres for motion and sensation, and for consciousness, the medulla oblongata and the spinal cord may all be involved in the action of this poison.

Again, alcohol must be ranked with those narcotics which, after long-continued use, leave behind them permanent and enduring changes in the bodily organs. These changes may not always be recognizable by the minute anatomist, but they may be known very unequivocally by persistent anomalies of function. We know that the system accustoms itself to the poison. In other words, a certain tolerance is established, so that doses originally potent gradually cease to produce the same effect upon the nerve-centres. As the poison is the same as it ever was, this tolerance must be founded in a permanent change in the vital activity of the organs concerned. Besides its action on the nervous system, or animal life of the individual, alcohol has most indisputably an influence on the vegetative life. It affects the circulation and the processes of nutrition. Every-day experience teaches us that the habitual moderate enjoyment of alcohol encourages a tendency to corpulence. Liebig, who asserts that we have here a diminishing of the processes of oxidation, has explained this fact by the well-known hypothesis we have quoted above. But there are other facts which force us to conclude that alcohol most powerfully affects the metamorphosis of tissues. There is a long series of authors who have noted, though not with all the scientific accuracy desirable in such matters, that the excretion of carbonic acid is diminished after the use of alcohol. v. Boeck and Bauer[1] have recently established this fact in dogs by an experimental method which seems free from objection. There is, however, this limit, that only small quantities of alcohol

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[1] Zeitschrift für Biologie. X. 1874.

diminish the excretion of carbonic acid. Larger doses, on the contrary, considerably increase this excretion. The latter circumstance is explained, according to v. Boeck and Bauer, by the great state of muscular excitement and jactitation (Muskelunruhe) into which the animals were thrown by larger doses. These authors believe that we should see diminished excretion of carbonic acid, even after large doses of alcohol, if we could do away with the increased muscular movements; and if, as happens in human beings, large doses of alcohol were followed by deep sleep. The experiments of Boecker (loc. cit.) and Rabuteau[1] are equally in favor of the view that alcohol diminishes tissue-changes; for they found that the excretion of urea was also diminished by the use of alcohol. To the same effect are a long series of observations on the effects of spirits of wine on the temperature of the body. Unfortunately, many of the observations are wanting in that nicety of observation which could entitle them to rank with those facts which may be considered as placed beyond dispute. Still, sufficient is known to indicate the direction in which our inquiries may be extended. If all these observations relating to the excretion of urea and carbonic acid and the lowering of temperature should be confirmed, there could scarcely be room for doubting any longer that alcohol diminishes the forces concerned in tissue-metamorphosis. Bonwetsch's discovery of the retardation of [the changes in] oxyhæmoglobin by alcohol would then afford a satisfactory explanation of the whole affair.

It is only when large and poisonous doses of alcohol are taken that the temperature of the body is very sensibly depressed, so as to amount to several degrees of the Centigrade (100°) scale. With moderate doses the reduction of temperature is far less, and scarcely amounts to 1° Centigrade (1.8° Fahr.). Obernier,[2] and Parkes, and Wollowicz (loc. cit.) were scarcely able to demonstrate any effect on temperature from small doses of alcohol. Whilst Dumeril and Demarquay,[3] Lallemand, Perrin, and Duroy (loc. cit.), Ruge,[4] Bouvier,[5] Mainzer,[6] Sulzynski,[7] Daub,[8] and Riegel,[9] all observed slight falls of temperature.

[1] L'Union méd. 1870.
[2] Pflüger's Arch. 1869. II.
[3] Archiv. général. IV. Sér. XVI. 1848.
[4] Virchow's Archiv. Bd. 49. 1870.
[5] Pharmak. Studien über den Alkohol. 1872.
[6] Inaug.-Diss. Bonn. 1870.
[7] Inaug.-Diss. Dorpat. 1865.
[8] Med. Centralblatt. 1874.
[9] Archiv für klin. Med. XII. 1874.

Alcohol has also unmistakable effects on some of the organs of vegetative life. Its influence on the movements of the heart is placed beyond doubt, as regards human beings, by the experiments of Parkes and Wollowicz (loc. cit.); and as regards animals, by the experiments of Zimmerberg (loc. cit.). This influence is at first a considerable increase in the energy of the heart, which soon becomes greatly diminished. How far the different cardiac nerves are severally concerned cannot be settled off-hand. It is quite clear also that the vascular system is not exempt from the action of alcohol. The reddening of the skin, as well as the sinking of the blood-pressure after the injection of large quantities of alcohol, both point to a considerable diminution of the tone or tension of the arteries (arterial tonus).[1] There is a pretty generally diffused opinion that alcohol, in a reflex manner (by irritation of the sensitive nerves), excites and increases the secretions. It is in this way that it is credited with improving digestion. Nearly all our text-books of medicine speak of increased secretion of gastric juice as one of the effects of alcohol. But Claude Bernard's experiments [2] have shown that strong alcohol has exactly the contrary effect. In other words, it brings about a diminution of all secretions, whilst they are but very slightly increased by very dilute spirits of wine. This is very strikingly so as regards digestion. Claude Bernard found that he could check digestion in the stomach of a dog in whom that process had commenced, by introducing alcohol into the stomach; and if alcohol and food were given together, digestion began a little later than in animals who had taken no alcohol. The secretion of gastric juice is therefore almost entirely suspended for a time by spirits of wine. Bernard has demonstrated the same as regards the activity of the secreting glands of the intestines. The excretory functions of the kidneys are decidedly increased and accelerated by the ingestion of moderate quantities of alcohol. Even the laity are familiar with the diuretic action of alcoholic liquor.

The local action of spirits of wine may be partly explained by

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[1] Compare on this point *Parkes* and *Wollowicz*, *Zimmerberg* (loc. cit.) and *Tscheschichin*, Archiv für Anat. med. Phys. 1866.

[2] Leçons sur les effets des substances toxiques, p. 414.

the behavior of this substance with albuminous bodies, and by its affinity for water, of which we have spoken already. Its local action, however, must clearly be due in part to the direct contact of the alcohol with the terminations of the sensitive nerves. For instance, if the spirit be very strong and applied to certain parts, there is more or less of intense burning pain. There is then almost immediately (by reflex action after the irritation of the sensory nerves) dilatation of the blood-vessels and increased flow of blood to the part—symptoms which may, if the irritation be continued, go on to exudation and the formation of sores, and may even go on to typical inflammation, just analogous to the effect of epispastics.

As regards chronic alcoholic poisoning, or the effect of long-continued doses of alcohol, a number of experiments have been made on animals. Magnan[1] fed some dogs for some months with alcoholic liquors, and he gradually saw symptoms analogous to those of chronic alcoholism in human beings developed in these animals. The dogs suffered from gradually increasing muscular weakness, general tremblings, and, especially during the night, from hallucinations (?), which were generally recognized by yelling out, howling, and symptoms of extreme fear. They gradually sank from a sort of chronic marasmus. Kremiansky[2] instituted analogous experiments, in which he specially directed his attention to the development of a hemorrhagic pachymeningitis. Magnan's results in this direction were negative. He thus differs from Kremiansky and Neumann,[3] who were able to demonstrate the pathological changes mentioned above in the dura mater in dogs.

The etiology of alcohol-poisoning is very closely connected with the abuse of spirituous liquors. The most popular of all methods of intoxication is simply acute alcoholic poisoning—drunkenness in its various degrees. Cases of chronic alcoholism must also be referred to the voluntary use of alcohol. It is indeed in very rare cases, and they are growing still more rare,

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[1] De l'alcoolisme des diverses formes, etc. Paris, 1874.

[2] Virchow's Archiv. 1868. XLII.

[3] Inaug.-Dissert. Königsberg. 1869.

that we see alcoholic poisoning produced either by pure accident, or from criminal motives. Mild forms of intoxication may indeed result from the common application of alcohol or spirits of camphor as a surgical application to wounds, as is commonly done in France. Schlesinger,[1] indeed, noted a case of delirium tremens in a lady who used a great deal of eau de Cologne. [It is well known that this perfume is often mixed with water, and taken as a beverage.—TRANS.]

In consequence of the widespread use of alcoholic liquors as beverages, the baleful effects of this poison are not confined to individuals. They affect, and are felt by, whole communities. They are therefore deserving of notice, not merely from medical men, but from statesmen and political economists. Accurate statistics, which should show on the one hand the amount of alcoholism in different countries, and on the other side the diseases and crimes which are connected with or dependent upon it, would enable us clearly to see the enormous material and moral injury done by this poison. Unfortunately, much of the material is as yet uncollected. Enough has, however, been done on a small scale to give us an idea how such inquiries would be answered. In England, where special attention has been given to such questions, 75 per cent. of all crimes and 25 per cent. of insanity are closely connected with the abuse of alcohol. It is still worse as regards Ireland. It has been ascertained that in Glasgow every three-and-twentieth, in Liverpool every twentieth, and in Dublin every tenth person accused was found in a condition of drunkenness.

The consumption of spirituous liquors is generally larger in northern countries (Russia, Sweden, England, the north of Germany) than it is in southern countries (the south of Germany, Italy, and Spain). Hermann[2] has given us some interesting accounts regarding Russia, and St. Petersburg in particular. The removal of the brandy monopoly in 1863 caused an enormous increase in the diseases which are due to alcohol. In the five hospitals of St. Petersburg, in the years 1861–1865, 3,206

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[1] Casper's Wochenscrift. 1835.

[2] Petersburg med. Zeitschr. XIII. 2. 1867.

patients were treated for alcoholism, or 1–3 per cent. of all the patients. Whilst in the years 1861 and 1862 (before the removal of the monopoly) some 26 and 23 cases respectively were fatal from alcoholism, these numbers rose, in the three years following the removal of the monopoly, to 33, 102, and 89.

Of late years the consumption of the liquor called absinthe has reached enormous proportions, particularly in the large towns. The percentage of alcohol in the beverages consumed is naturally a point of special interest, for all those countries where the use of brandy prevails, afford, in consequence of this, a larger contingent of cases of alcoholic intoxication than those where beer and other beverages poor in alcohol are the staple drinks.

As regards the various ranks of society, the rule is that an overwhelming majority of drunkards is drawn from the lower classes—the proletariat and artisans. There are, however, no very accurate statistics on these points, and we know that drunkenness occurs far too commonly among the educated classes. Hermann says that in St. Petersburg the majority of drunkards are not taken from the very lowest class, but rather from the ranks of clerks and officials of the lower grades and small traders. In the year 1862, for example, among 109 alcoholic patients, 44 were clerks, 40 artisans, and only 20 day-laborers. In the year 1863 (in which the brandy monopoly was removed), among 297 patients, 107 were clerks, 99 artisans, and 32 day-laborers.

It is easy to understand why the male sex is more commonly given to alcoholism than the female. (Of the 3,206 cases collected by Hermann, only 400 were women, or about one-eighth.) It is also natural that children and very old people less often suffer from alcoholism than people in middle life, or, in other words, between thirty and fifty years. Nothing definite can be laid down as regards the quantity of alcohol required to intoxicate, except as regards concentrated alcohol (over 50 per cent. in strength). As a rule, very small quantities of this are enough to bring on symptoms of poisoning in a very short time. In children, two tablespoonfuls of alcohol of 60 per cent. strength

has proved a fatal dose.[1] In grown-up people not accustomed to stimulants, a larger quantity of rum or arrack (from one and a half to three fluidounces) will be required to rapidly produce symptoms of intoxication. Absolute alcohol (over 90 per cent. solutions), under all circumstances, even in small quantities, produces symptoms of poisoning by its local action.

The symptoms and course of poisoning by alcohol are peculiar from the variety and complexity of the phenomena.

In order to facilitate the study of these, we divide the subject as follows:

I. Acute alcoholic poisoning. (*a*). Drunkenness (or mild form). (*b*). Poisoning by larger doses of alcohol (severe form).

II. Chronic alcoholic poisoning. (*a*). Delirium tremens. (*b*). Chronic alcoholism.

I. (*a*). Drunkenness. Familiar and well known as this condition is, we must, for the sake of completeness, give a brief account of it here. The primary pleasant effect of moderate quantities of alcohol, and it is to these it owes its great popularity and extended use—is a sort of amiable (wohlthätig) alteration of common sensations—an exalted cerebration—more facile association of ideas—a feeling of increased bodily strength—and the banishment or vanishing of all previously present unpleasant sensations in the domain of both bodily and physical life. The expression to be "elevated" (angeheitert sein) capitally describes this condition, which can scarcely in itself be considered an abnormal state (yet is so for the individual at the given time). Generally speaking, this condition leaves no unpleasant consequences behind it. The quantity and quality of the alcohol required to bring about this simplest form of poisoning varies greatly according to the individuality or personal character of those who take it. Only a very little more of the poison (alcohol) requires to be taken, and the person already under its influence is immediately lost to propriety. The state previously described is now greatly exaggerated. The man expresses his opinions more loudly and more freely, the tendency to put all his feelings into words becomes more and more uncontrollable,

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[1] *Deutsch's* case. Preuss. Vereinzeitung; quoted in Schmidt's Jahrbuch. Bd. XXV.

and the cerebral centre, which should control his actions and his words—that "prudent, cautious self-control" which (according to Burns) is "wisdom's root," and gives to the sober the stamp of rationality, becomes weaker and weaker. The uncontrolled combination of ideas, the unfettered imagination, causes a flood of words, without arrangement, to roll over the tongue in a ceaseless torrent. The hidden "I"—the whole man, willingly or unwillingly, comes to light, and the sober spectator and listener often gets unexpected glimpses of those depths of the soul's inner life which the man at another time would most anxiously screen from the gaze of the world around him. At the same time the excitation of the motor centres—the exaggerated tendency to action—often keeps pace with the general excitement, and urges on the drunken man to purposeless exhibitions of strength, often impelling him to seize hold of the living or lifeless objects which surround him. All the passions press to the front, without any concealment and with exaggerated intensity; love, hatred, revenge, fear, and anger lend their changing colors to the uncontrolled impulses which urge him on. But the overstrained bow is easily broken—often with a sudden snap. The hurly-burly is hushed, and the drunken man falls into a state of deep coma or narcotism. All the symptoms of excitement are weakened, and are succeeded by almost complete paralysis, and the over-stimulated and excited organs refuse to do their duty. This description, naturally enough, is not always accurate, but it pretty fairly represents the general symptoms of intoxication. It is not possible, in our limits, to include all the varieties met with in practice. It must, however, be noted that in some cases the effects of alcohol are diametrically opposite, having a depressing effect upon the individual who takes it, even from the very first, making him reserved, tranquil, and even secretive, and he goes on to a state of narcotism without any of the ordinary outward signs of drunkenness. The amount of consciousness and rationality retained by the drunken man varies greatly, and is by no means always proportioned to the quantity of poison imbibed. Men who are manifestly drunk, often act and transact business, though perhaps only for a brief time, with complete reflective faculties and with a good deal of consideration. It is just the

same as regards the memory of what took place in the drunken state. No rule can be laid down, for some remember everything perfectly when they awake, others have no recollection of anything.

The bodily condition during drunkenness, and the narcosis which follows, exhibit the following peculiarities: the face of the drinker becomes flushed and reddened, so do the ocular conjunctivæ; the pulses beat more forcibly,[1] the skin is often profusely bathed in sweat, the frequency of the pulse is increased, and the pupils are, for the most part, contracted. The quantity of urine is generally increased and its specific gravity diminished, especially when much water has been ingested with the alcohol. The movements of the voluntary muscles, which were at first considerably increased in energy, become at a later stage decidedly less powerful, and a diminished power of co-ordination of movements becomes specially evident.

The drunkard speaks stammeringly, staggers, and easily falls to the ground. It is very common to have repeated vomiting before narcotism sets in, but this symptom may be entirely absent. In the comatose condition, or full narcosis, the faculty of responding to external impressions—in other words, reflex action—is weakened in various degrees, and sometimes, in very deep intoxication, entirely lost. The dead-drunk man lies with relaxed and limp limbs, perfectly motionless, breathing deeply, but seldom. The pulse is now generally small and quick, the skin cool, and covered with clammy sweat. It is with great difficulty, if at all, that any sign of consciousness can be elicited by loud calls, shaking, sprinkling with water, or other modes of irritation. As a rule, he awakes spontaneously, after sleeping for a varying time, with different kinds of sequelæ of his excesses. Then he feels a severe, oppressive headache, finds it difficult to think, for his ideas are all at sixes and sevens; and at first he has scarcely any recollections of his recent debauch. Very commonly symptoms of acute gastric catarrh come on. Severe vomiting sets in, which often lasts for some days, and

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[1] *Mendel* (Virchow's Archiv. Bd. L.) found the temperature of the head, in drunkenness, higher than that of the rectum.

occurs several times in the same day; he has complete loss of appetite, great thirst, an unpleasant taste in the mouth, and in addition, a great feeling of weariness and muscular prostration, felt all over the body. We have thought it better thus to sketch the general features presented by drunkenness, than to describe the spontaneous and often arbitrary varieties of one and the same condition under special names, and in great detail.[1] Drunkenness is in its essence nothing else but a transient insanity. It may assume almost any form; and indeed all the forms assumed by true insanity are imitated with great accuracy in a manner well worthy the study of those who devote themselves to psychology.

Since the time of Percy,[2] French authors have specially noted a form of drunkenness under the name of "convulsive intoxication" (ivresse convulsive). It is distinguished from the ordinary kind by severe general convulsions and maniacal delirium. The attacks generally come on some hours after the person attacked has drunk heavily. They occur during sleep, and often without any clear symptoms of drunkenness having previously manifested themselves. Two powerful men could scarcely restrain the patients, who showed fight, and several of these attacks have ended fatally by the patients springing out of windows. In fact, the whole description is that of an acute attack of mania. The bodily condition differs very little from that common in the usual forms of drunkenness; sometimes, however, general anæsthesia has been noted. According to Percy, this convulsive intoxication may occur in very sensitive or "irritable" people, after any great excess of devotion to Bacchus; but it is especially common after the use of new wine fortified with corn-spirit, or old wines adulterated in the same way.

I. (*b*) The symptoms are, however, considerably modified in those cases where large quantities of strong alcohol are introduced into the system at one time. In these cases there is generally no stage of excitement observed, but from the very beginning the signs of profound general depression of all the vital

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[1] Compare *Falck*, Intoxicationen, in Virchow's Pathologie und Therapie. II. 1, 2.

[2] See *Percy*, Diction. des sciences méd. t. XXVI., and especially *Magnan* (loc. cit.) and *Lallemand*, *Perrin*, and *Duroy*, loc. cit.

functions are present. In this category most of the criminal cases of alcoholic poisoning will be found. Many cases are recorded in books and periodicals where children of a few months old, up to eight years of age, have been purposely killed in this way. There are also many analogous cases in grown-up people, who for the purpose of beastly gratification of appetite, have gone on imbibing strong spirits till they sank insensible to the ground. [Such cases are common in the docks, and are known as "sucking the monkey."—TRANS.] It is usual to find the persons thus poisoned in a state of deep coma and unconsciousness (sopor), with various degrees of general anæsthesia, with deep, stertorous respiration, small, rapid, and easily compressible pulse, and, as a rule, dilated pupils, insensible to light. The skin of the face is generally reddened and bloated-looking, but sometimes cyanotic; the skin of the trunk and extremities cool and covered with clammy sweat. The mucous membranes of the mouth and throat may show similar changes as in mild cases of poisoning by acids, especially a whitish coloration of the swollen and spongy epithelial lining. Vomiting, though often noted, is by no means a constant symptom. Many of the recorded cases mention the passage of thin, slimy stools, mixed with blood. In very young patients (children under three years of age), this sort of poisoning may terminate in death in a very few hours—it is, however, usual to find this preceded by general, or sometimes purely local[1] convulsions. The older the children are, the more likely is it that remedial measures will avert death. The symptoms in grown-up people are strictly analogous. Here, too, it is usual to find the patient in a condition of the deepest stupor; and in many of the recorded cases it is expressly stated that the patient fell down insensible whilst drinking. Consciousness is generally entirely abolished, and it is the same with sensation. The skin is cool, and the face and mucous membranes are cyanotic. If these dead-drunk people remain long on the ground in this condition, acute gangrene is sometimes seen on those parts of the skin most exposed to pressure. The epidermis is first raised in blisters, which are filled with blood-stained

[1] Thus, in the case previously quoted from *Deutsch*, convulsions were noted only in the right side of the body.

serum, just as in burns, and the case may go on to the formation of a line of demarcation, and actual dropping off of portions of the body. The surrounding surface is highly œdematous, swollen, and red, just as in phlegmonous erysipelas.

Mitscherlich relates a case of this kind.[1] The man fell down, and lay thirty hours with his left arm under him. The hand became gangrenous, and the whole of the left arm was highly œdematous, swollen, and reddened.

In these cases, too, the breathing is deep, stertorous, and intermittent; the pulse small, and scarcely to be felt. The extremities are of marble coldness, and the temperature of the whole body is considerably lowered. In the most severe cases of this kind the pupil is dilated, and does not respond to light. In less severe ones, especially when some traces of consciousness are still present, the pupil is contracted to a pin's point.

Burkitt[2] describes a case, in which the previously contracted pupils dilated for a moment whenever the unconscious patient made attempts to speak.

It is very common to find both the eyelids and conjunctivæ with livid blood-spots (suggillirt). The eyeballs are sometimes very prominent and staring—sometimes deeply sunk in the orbits. Local symptoms of any disorder of the digestive organs are not usually much marked at first during the comatose condition—and begin to appear at a later stage, if the case have not ended fatally. In the mouth, except a very strong smell of alcohol, and a dry, fissured red tongue, covered with a thick fur or scab, there is notning very remarkable. Vomiting of blood, and stools containing blood have been noticed in a very few cases. Sometimes the stage of complete coma alternates with either furious or frisky delirium; and convulsive movements of single groups of muscles, or extending over the whole of some region of the body, and even general clonic spasms, are not infrequently met with.

The duration and course of these conditions are very varied, especially so as the treatment, or attempts at recovery, have been

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[1] Virchow's Archiv. Bd. XXXVIII. 1867.

[2] Dublin Medical Press. 1839. Quoted in Schmidt's Jahrbücher.

begun early or delayed till a late period. Loss of consciousness and coma may last several days, and may then terminate by the supervention of favorable symptoms, or may pass into a condition very similar to delirium tremens. If no efforts be made at recovery for a considerable time, death may occur very easily in the first stage, in consequence of asphyxia and paresis of the heart. But death may also occur in the later stages. In the cases which begin to improve, the patients become conscious after some time, and then complain of violent headache and general weakness, and they labor for a considerable time under the symptoms of a more or less acute gastritis, which specially shows itself in frequent retchings and vomiting, pain in the epigastrium, total loss of appetite, and other symptoms of the same class.

Post-mortem examinations of the bodies of those dying from acute alcoholic poisoning exhibit in some instances an exceedingly prolonged and remarkable resistance to putrefactive processes;[1] but the opposite has also been noted, namely, an exceedingly rapid development of decomposition (compare Mitscherlich, loc. cit.). On those parts of the skin most subject to pressure during life (shoulders, nates, etc.) very large post-mortem stains or ecchymoses will be found; sometimes the epidermis is raised into blisters, or there may even be more or less advanced bed-sores (decubitus). The mucous membrane of the digestive tract will sometimes have contents smelling plainly of the poison, while at other times there will be no trace of alcoholic odor. These mucous membranes will sometimes exhibit only redness and swelling, sometimes there will be ecchymoses, very seldom ulcers.

Pennetier[2] observed that ulcers were beginning to form in the lower part of the œsophagus and in the stomach in a fatal case of poisoning by alcohol. The mucous membrane of the respiratory tract exhibits a widely-spread and intense injection of blood-vessels; the lungs themselves are very often found in a

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[1] In the case previously quoted from *Devtsch*, in spite of a very hot summer, no sign of putrefaction was found as long as thirty-six hours after death.

[2] Thèses. Paris. 1865.

state of œdema; still more frequently we discover in their posterior and inferior portions hypostases and hepatization. The smell of alcohol can nearly always be detected in the abdominal cavity. The same is affirmed of the cranial cavity, in which also serous exudations and great injection of the meninges are usually found. There are no other characteristic appearances in the brain.

II. The condition known as general *chronic alcoholism* exhibits a variety of differing symptoms, which sometimes alternate with one another. If we were to comprehend all the pathological changes which occur in notorious sots, we should have to make numerous subdivisions and distinctions in order to facilitate the study of a subject on which so many mistakes have been made by both ancient and modern writers.

It appears to us essential to declare at the very onset that in a number of cases chronic alcoholism is perfectly identical with other forms of disease. In other words, that the poison of alcohol, either alone or combined with other pathological causes, produces bodily or mental diseases which in themselves afford nothing characteristic of the effects of alcohol. To this category belong many cases of imbecility, of paralytic dementia, and of melancholia, as well as of tabes dorsalis, atrophy of the liver, morbus Brightii, and other diseases which we often find described as special forms of alcoholism without any claim, in our opinion, to such a designation. We shall gain far more insight into the whole question if we start with the proposition, that besides the special diseases resulting from this poison, the habitual misuse or abuse of alcohol is one of those primary causes which combine together to generate a great many forms of disease.

In this place, however, we are chiefly concerned with those diseases which are more or less characteristic of alcoholic poisoning. The changes and maladies of the digestive organs, such as gastritis with or without jaundice, cirrhosis of the liver, etc., though very commonly the consequence of chronic alcoholism, must be treated separately in other portions of this work, under special sections of pathology and therapeutics. In this some-

what restricted department there are consequently only two truly characteristic groups remaining, namely:

1. *Delirium tremens*, which is essentially the acute form of chronic poisoning by alcohol; and

2. *Chronic alcoholism*, properly so called, consisting of a complexity of symptoms of a general diseased state of the nervous system, involving both mind and body.

Here, too, it must be admitted that even these two groups very often resemble and may be confounded with other forms of disease, so that their right to a separate place in our nosologies may sometimes be very fairly disputed. In the true sense of the terms, the effects of alcohol are no more specific than those of any other poison.

II. *a.* The term "delirium tremens" was first introduced into pathological literature by the English doctor Sutton,[1] in the year 1813. This author marked as a special character of delirium tremens that, unlike other acute forms of delirium, it was not improved, but rather made worse, by bleeding; but on the other hand it could be cured by opium. He lays no stress on alcohol as the pathogenetic agent or prime factor in the disease. This was first specially insisted upon by Rayer in 1819, who proposed the name "oino-mania" for it.[2] However, the original name has held its ground, and is now commonly known, not only to the medical profession, but even to the general public.

With regard to the true etiology of delirium tremens, two rather opposite opinions have long been held. According to the first view alcohol itself is the immediate cause of the delirium, since it acts as a special irritant or stimulant to the brain and nervous system. This, the so-called toxæmic theory, is almost universally accepted in France and Germany, and is becoming so in England also. The question has been discussed with much warmth in that country by such men as Peddie, Anstie, Laycock, Hughes-Bennett, Gairdner, and others. Other observers, who base their view on the proposition that the delirium breaks out

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[1] *A. Foville*, Du delirium tremens, de la dipsomanie, et de l'alcoolisme. Notice historique et bibliographique. Archives générales de médecine. VI. S. Bd. X. 1867.

[2] Mémoire sur le delirium tremens. Paris. 1819.

first just as the soaker is deprived of his alcohol, contend that the withdrawal of the accustomed stimulus, and thus the withdrawal of the poison, is the true and real cause of the outbreak of delirium (Cuming[1]). They hold that the nervous system, weakened by the long-continued operation of the alcohol, cannot tolerate the removal of the customary stimulus without suffering a tumultuous disturbance of its equilibrium. And this disturbance occurs just as the alcohol is suddenly withdrawn from the system. According to this view, therefore, delirium tremens is a sort of delirium of inanition. Cuming supports this view by a long series of carefully observed clinical facts, and he does not dispute the possibility of a delirium produced by acute alcoholic poisoning.

Other authors, to reconcile these conflicting views, propose to recognize several varied forms of delirium tremens. Thus, for example, Marston[2] recognizes a delirium ebrietatis, which develops itself immediately after a single great excess or debauch, in opposition to a delirium potatorum (of habitual sots). In the first case the alcohol itself, in the latter its withdrawal, would be the proximate *causa morbi.* Hermann (loc. cit.) has noticed that true delirium tremens more commonly occurs after some great excess at one time, whilst long-continued drinking (the so-called "quiet sotting") more commonly induces a condition of chronic alcoholism with paralysis. Sander[3] also has noticed cases in which the delirium potatorum seemed to originate in a solitary debauch. It is a matter of old clinical observation that the delirium of sots shows a sort of preference for injuries (such as fractures and dislocations), and for the intercurrent internal diseases of soakers (such as pneumonia). Here the external surroundings, for the most part, naturally make a great change in the whole mode of life of the individual who is accustomed to take spirits freely.

It is very difficult to hold the balance evenly in such controversies. Indeed, it seems probable that both views have some

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1 On delirium tremens. Dublin Quart. Journal of Med. Science. No. 98. 1870. p. 62.

2 Edinburgh Medical Journal, Oct. 1860.

3 Archiv für Physchiatr. und Nervenkrank. 1868.

truth, and that both alcohol itself and its [sudden] withdrawal may both be factors in different cases of this disease. But the clinical cases and observations which lie before us do not favor the theory propounded by Marston of varied forms of delirium tremens, according to the cause—since varying causes, in this instance, do not seem to produce any variety, or at all events not a corresponding variety, in the symptoms—for delirium tremens is essentially the same under all circumstances.

Magnan (loc. cit.) distinguishes the following various degrees of intensity in delirium tremens (délire alcoolique):

1. Simple delirium tremens (délire alcoolique afébrile).

a. Slight form, terminating quickly in recovery.

b. More severe form, with more tedious restoration to health, and great tendency to relapses. Particular delusions based on persistent hallucinations are obstinately persisted in. Suicidal tendency.

c. Delirium tremens in people with hereditary predisposition to psychosis. Great impressionability; long duration of attacks; imperfect recovery. Very slight excesses induce slight relapses.

2. Febrile delirium tremens.

The outbreak of this disease is always more or less sudden. Well-characterized prodromal or premonitory symptoms are not known. Occasionally it is preceded by a similar prodromal stage of melancholy, though a shorter one, to that which precedes true attacks of insanity. As a rule, the scene opens with the well-known specific hallucinations of vision common to topers. For the most part they see little dark animals (beetles, rats, birds, serpents, and the like) wherever they turn their eyes. But they are also very often troubled in addition by other horrid images, which sometimes assume the form of the devil, sometimes of a policeman, or of great black beasts, and the like.

Magnan (loc. cit.) considers that the hallucinations of topers are especially characterized by their mobility, as well as by their horrid nature. Delirium tremens is never filled with stiff, fixed visions.

In the hallucinations of the sense of hearing, dreadful sounds predominate, although the patients sometimes hear music, and songs, or other pleasant things. Besides all this there are a variety of abnormal sensations, apparently due to anomalies of

the sense of touch and of cutaneous sensibility. The patients will believe that they are enclosed in a fine net of spun glass, or of some textile fabric. All sorts of little insects are crawling under their skin—these sting and torment them—or they have some other delusions of similar kind. At a little later period a peculiar restlessness attacks the voluntary muscles. The patients are continually making little objectless movements with their fingers. Lying in bed, they drum continuously with their fingers on the counterpane, reach out all round them with their hands, as if they would move away some small objects. They have always a very unsteady look—a sort of wild appearance. Sometimes they have even nystagmus. But they seldom entirely lose consciousness, or only for a very brief interval. The patients know where they are and who is with them, and for the most part they answer questions correctly. Very often the last scene in the recent debauch, such as a quarrel, etc., is repeated, sometimes half-aloud, sometimes in a noisy delirium ; and sooner or later, along with increased restlessness, there is more or less fierce mania and fury. Delirium tremens differs from mere intoxication in this, amongst other things, that the general deportment and aspect of the patient almost always assumes a character of depression. The delirious patient is worried by his hallucinations, and most of his violent acts are done with the object of freeing himself from his tormentors. It is very rare to find the cheerful, hilarious deportment which is characteristic of some forms of mania, and of the earlier stages of intoxication. Cheerful delirium is more commonly met with in patients who suffer from pneumonia or some other febrile affection, as well as from delirium tremens.

Occasionally we find well-marked delusions as to persecution, in which the devil, the police, and similar objects of terror to common men, play the chief part—they imagine that they are being pursued by these objects. It is not uncommon to find the patients inclined to fight those about them, and they are often very mischievous and destructive. These symptoms are usually exacerbated at night, and there is much more dread then than at other times. Complete inability to sleep is also a symptom which is never absent. Another somatic symptom is the tremor,

which varies both in extent and intensity, and may even be absent altogether. The face is generally flushed, the conjunctiva injected, and the patient usually perspires very freely. The patient looks very feverish. It is easy to understand that accurate thermometrical observations are not easy to take under such circumstances, and we have, therefore, no very reliable information on this point.

The duration of delirium tremens is limited to a few days in the great majority of cases—at the most it extends to a fortnight, whilst the disease is at its height. There is delirium even in the daytime, it grows worse when twilight begins, and is most severe at night. On the other hand, when convalescence commences, one of the first signs of improvement is freedom from delusions during daylight. During the evening hours and in the night the patient is still more or less troubled with a return of the hallucinations, until at length, after he has enjoyed tranquil sleep for a few nights, he may be regarded as quite cured.

If there are surgical complications, or some internal malady complicate the case, the course of the disease is often very unfavorable, and death may occur as early as in the first week, with all the symptoms of asthenia. Every practical surgeon knows, from his own experience, that the prognosis of cases of pneumonia or fractures, complicated with delirium tremens, is a very unfavorable one.

Magnan, in his recent work on Alcoholism, in addition to the ordinary form of delirium tremens which we have just described, mentions a severe febrile form which very commonly runs a fatal course in a very few days. The fever in such cases, according to Magnan, is not so much dependent upon any internal or external complications or symptoms, but must be regarded as idiopathic. Up to the present time he has published seven cases of this kind, which were remarkable, not only for the high fever (temperature of 42° C. = 107.6° F.), but also for the very severe tremors which extended all over the body, and continued even in sleep. These tremors could be plainly felt by the hand in almost every region of the body. Besides this, the "febrile delirium" is characterized by extreme muscular weakness, and the pulse, which is slow at first, becomes much quickened later on,

and is extremely weak. Sometimes there is albuminuria. Finally death occurs, with symptoms of extreme general asthenia. The special etiology of this form is as yet unknown. Yet it is known to follow repeated and recent excesses (unlike the delirium tremens which follows accidents or intercurrent diseases—the so-called traumatic delirium of many authors).

It is not possible to describe here in detail all the modifications of symptoms met with in different cases of delirium tremens, which deviate in different ways from the sketch just presented to the reader. It should, however, be noted that tetanic and eclamptiform convulsions have been observed in some cases.

It is very rarely that we find a man attacked only once by this complaint, unless, indeed, the first attack has proved fatal. It is far more common to see the same patient come again and again to the hospital, at longer or shorter intervals. The deleterious effects of alcohol on the nutrition of the tissues cause the intervals between the attacks to become shorter and shorter in most cases, because the patient after each attack has a lessened store of bodily and mental power to sustain him. So, unless death speedily closes the scene, the patient gradually settles down into the ranks of the demented and paralyzed, and sooner or later succumbs to marasmus. In the bodies of such patients we find signs of varied and severe chronic diseases of the stomach, pigmented and thickened mucous membranes, the liver most frequently in a state of fatty degeneration, and the kidneys are sometimes in a similar state.

Pachymeningitis is also a common condition, especially when several attacks of delirium tremens have occurred. The pia mater is found more than normally adherent to the superficial cortical layers of the brain, and the brain itself is described by several observers as more than usually dry and anæmic.

II. *b*. It is far more difficult to describe within a moderate compass the varied forms of "chronic alcoholism," properly so-called. It is without exception the consequence of long-continued and continuous abuse of spirits, through which the body is gradually and systematically accustomed to larger and larger quantities of the poison; and the whole system, down to its very

foundations, is shattered and shaken. Those who belong to this category are very seldom seen in a state of actual drunkenness in the later periods of their wasted lives—in fact, at those periods which concern us at present. They follow their businesses or professions, or exercise their trades with a constantly and rapidly diminishing remnant of their physical and moral powers, and are compelled to sustain these extremely tottering bodily powers by constantly increasing quantities of alcohol.

Some of these habitual sots are attacked by and succumb to diseases of a casual kind, which present no symptoms characteristic of chronic alcoholism. We need not therefore concern ourselves with these. But other habitual soakers suffer from symptoms which cannot be clearly identified with any of the known and recognized diseases in our nosologies.

In the first place we must mention a number of psychical disorders, which are, if we may say so, specially characterized by their want of character or want of individuality—reminding us of the "moral insanity" which has lately given rise to so much discussion. In such cases we really do not know if the craving for drink, the alcohol mania, be the original cause of the malady, or whether we must regard the craving as itself one of the symptoms; unless, indeed, we have watched the development of the disease from its very beginning. Continual struggles with temptation, and continual yieldings to it, reduce the man who was, perhaps, at first a well-meaning person, to a state of irreconcilable conflict and dissension with himself, with duty, and with the world around him. Although at first their intellectual powers are as strong as ever, such persons suffer severely from great anomalies of the passions and affections, and from a condition of deep melancholy, which is often associated with a tendency to kill themselves; and they strive to rid themselves of these feelings by a continual resort to their one remedy of fresh indulgences in alcohol.

Their power of resistance grows gradually weaker and weaker, whilst at the same time, step by step, their intellectual and physical powers grow more and more feeble. The man is now capable of committing crimes in order to satisfy the craving which is now his one ruling passion. In this category one often

finds men of position and eminence—high-class men in every sense. And just in proportion to the original development of what we may call the higher ethics, is the psychical conflict increased, and is the completeness of the moral ruin. Sots of the lower orders do not fall so low, because they have never climbed so high. In the few moments when the man is free to think, the very consciousness that he has ruined not only himself, but his family, becomes itself a fresh factor in the generation of fresh mental disorders, and assists the action of the original agent of mischief, the alcohol. The further course of cases of this kind is by no means uniform; very many, indeed, put an end to their own lives. Comparatively few are reclaimed in the long run. The great majority, indeed, perish by intercurrent diseases, or are attacked by general paralysis; or some one of the psychical anomalies from which they suffer develops into a dementia which is strongly tinctured with gloom.

A large number of the cases of so called *dipsomania* unquestionably belong to the class of cases which has just been described. Salvatori and Brühlkramer,[1] who first accurately described this form of insanity, and others of the earlier writers on the subject, referred the whole of the symptoms, including the craving for drink, to the abuse of alcoholic beverages. In later times, however, especially since Esquirol, writers on mental diseases admit that there may be other causes which bring about this condition and this craving, without excesses in drink having necessarily been indulged in previously—such causes, for example, as hereditary predisposition, grief and privations, loss of property, and the like.

There are, however, many points, even in such cases, of resemblance to those before described, especially as regards their first beginnings. All who have written on this subject agree in regarding a sort of cyclical course to be one of the pathognomonic signs of the disease. Dipsomania occurs in the form of a repeatedly recurring rage for drinking, which, according to the descriptions of the older writers, is preceded by very pregnant prodromal symptoms, particularly unpleasant sensations in the

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[1] For the history and bibliography of this subject, see *Foville*, loc. cit.

lower part of the abdomen, nausea, vomiting, want of appetite, and general depression. It is these premonitory symptoms which act as the proximal causes which drive the man to drink, which he continues to excess for a longer or shorter space of time, until either an attack of common insanity (Raserei) or general depression, combined with disgust at all spirituous liquors, puts an end to it for the time. In all these cases the sotting itself is the leading pathological symptom. In their further destiny these cases perfectly agree with the other forms of chronic alcoholism. This is not the place for any discussion of the question, whether *dipsomania* should be considered as a characteristic disease in itself. There is a great discrepancy of opinion in the literature of the subject. In the article by Cuming, quoted before, undoubted cases of dipsomania (periodic rage for drinking) are described as preceding all attacks of the common form of delirium tremens. Even Griesinger[1] remarks that this condition very often terminates in an attack of madness. As regards the etiology it must be owned that the number of cases in which there have been no previous excesses in Baccho is very limited.[2]

The closing scenes in the course of chronic alcoholism are so varied, that it is difficult to present a general picture of the whole disease. However possible or profitable it may seem to be to pick out a number of identical or similar cases for clinical observation, and thus to construct typical forms or groups of cases of chronic alcoholism, yet such a systematic semeiology does not seem justified in a scientific point of view, and may even prove dangerous, by seeming to support views which may after all be erroneous. In truth, there is little order or constancy in the grouping of the various symptoms. They may be mingled together in the strangest combinations, thus producing mixed forms, which would certainly lead any one who looked upon them as pathological entities, or as accurate typical forms of disease, into sad mistakes. Unfortunately, as regards chronic alcoholism, we have not yet a sufficiently firm foundation of anatomical

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[1] Die psychischen Krankheiten. Stuttgart. 1861.

[2] See also *C. With*, Ueber Dipsomanie Dissert. Berlin. 1869.

and pathological facts whereon to rear a systematic edifice. In order to get some direct ideas from this chaotic mass, it is very desirable, for the present, to sever as far as possible the psychical from the somatic or corporeal disorders. The psychical bear the general stamp of imbecility, and of persistent and general psychical decay, which manifests itself in various ways, and more or less actively. The general psychical degeneration extends to the intellectual powers as well as to the character of the patient. Both intelligence and character are stamped with feebleness, and this exhibits numerous gradations down to the absolute psychical nullity of apathetic dementia. This great variety in the behavior of the patients is to a great extent dependent upon the number and character of the delusions from which they suffer, and the erroneous notions which are founded on these by a large number of those suffering from chronic alcoholism. These, combined with the remains of the emotions or affections, the amount of which differs greatly in different patients, produce varied and anomalous forms or conditions of insanity: sometimes forms of exaltation with changing and absurd delusions, sometimes melancholic forms with religious mania, delusions of persecution, and the like, and sometimes mere tranquil dementia. It is not very uncommon for the steady downward course of this disease to be temporarily interrupted by maniacal exacerbations, which occur also in other mental diseases not caused by the abuse of alcohol. Such patients as we have now endeavored to describe are, as a rule, free from any very severe bodily or somatic ailments, and they form a large contingent in the population of our asylums. As might be naturally supposed, they are all perfectly incurable and hopeless cases. Another class, scarcely less numerous, is made up of those who suffer from various symptoms of the so-called general neuroses. A large number of these are included in the class of general paralytics. Here, in addition to the psychical symptoms characteristic of this condition (psychosis), we have different degrees of paralysis of motion and sensation. Paralytic dementia is one of the commoner terminal diseases of chronic alcoholism. We need not stop to describe this condition, since the symptoms are but little affected by the etiology. And besides these, apoplectic and epi-

leptic attacks may occur (intercurrently) in the course of chronic alcoholism. The apoplectic seizures are manifestly the basis of the "hemianæsthetic form" of chronic alcoholism, which Magnan (loc. cit.) describes from observation of ten parallel cases of the kind. The characters of this form are as follows: More or less complete loss of sensation (anæsthesia) of one-half of the body occurs in the course of chronic alcoholism in consequence of a more or less typical apoplectic seizure; sometimes this may be preceded by slight premonitory symptoms, such as headache, tingling sensations (formication), and giddiness. This loss of sensation is not confined to the skin merely. The mucous membranes (ocular and palpebral conjunctivæ, that of the nostrils, mouth, urethra, and anus) are also affected, so are the organs of sense (amblyopia and amaurosis); and deep-lying tissues, such as the muscles, are also affected. Paralysis (of motion) is at the same time more or less clearly pronounced; and may even improve, whilst the lost or impaired sensibility remains as before. The temperature of the affected side is often diminished by 2° to 3° Centigrade (=3.6° to 5.4° F.).

Magnan believes that these symptoms depend upon central disease (Herderkrankung) in the neighborhood of the thalamus opticus, of the corona radiata, and of the lenticular nucleus (of the corpus striatum); but apart from this we may have in the course of chronic alcoholism, in combination with any of the psychical symptoms named above, partial paralyses, anæsthesias, hyperæsthesias, cramps, and convulsions in various parts of the body. Of all the organs of sense, the eye is the most frequently attacked.

Galezowski[1] generally found well-developed dyschromatopsia in alcoholic patients. Of yellowish-green and bluish-green they could only distinguish the green; they confounded violet with red, and brown with gray. Magnan (loc. cit.) has repeatedly observed the same. Besides this, amblyopia and amaurosis occur in various degrees. Daguenet[2] investigated these conditions still more carefully. He found atrophy of the optic nerve

[1] Paris. 1868. Reference in Schmidt's Jahrb.

[2] Annal. d'oculist. 1869. LXII. Reference in Schmidt's Jahrb. 1869.

in many cases of disordered vision. The sudden commencement of weakened sight appeared very remarkable to him; everything round the patient seemed in a mist, so that even persons ten paces off could not be recognized, and so on. The patients saw better on dull days than on bright ones. They could not be trusted as to colors. The tint of well-known people seemed altered to them; sometimes they confounded gold coins with silver ones. There were very few objective symptoms with all this. The rather dilated pupils acted badly. At the beginning the ophthalmoscope only revealed a slight infiltration round the optic papilla, later on actual atrophy of the optic nerves.

Besides all these various disturbances of the nervous system, and all this disorder of the inner life of the man, it is very common to find the general nutrition of the body much altered by chronic alcoholism. No doubt, the chief cause of this is to be referred to the changes in the digestive organs—the chronic gastric catarrh alone being quite sufficient to prevent a proper and regular quantity of nourishment being taken, and making digestion, in the true sense of the term, almost an impossibility. But the dissolute mode of life of the patients and the psychical disorders themselves must also share the blame, and partly explain the gradual decay and diminution of the bodily powers and the great amount of emaciation usually present. It has been remarked already that many forms of disease, morbus Brightii, cirrhosis of the liver, and the like, may develop themselves in alcoholic patients, and thus help to bring about a fatal termination. Surmay[1] describes several cases of chronic alcoholism in which the patients died with symptoms of uræmia, but without albumen in the urine. But there do not seem to have been any very extraordinary symptoms; and as there were no post-mortem examinations, there seem to be no special reasons for making a new type of chronic alcoholism, under the name of the "uræmic form."

A few remarks must be made on the sexual functions in habitual drunkards, and on the influence of alcohol on generation. In the earlier stages, as a rule, the sexual functions are

[1] De quelques formes peu connues de la cachexie alcoolique, etc. L'Union Médicale. 19, 21. 1868.

very little altered, if at all, and it is only in the later stages that sterility attacks both sexes. It seems impossible to doubt any longer that the children of alcoholic parents not only exhibit, for the most part, a very great predisposition to psychical disorders, but that they also generally inherit a very badly-constituted nervous system. Indeed, it is asserted in books that children begotten in a state of drunkenness are epileptics from their very birth. Alcoholism in the father is worse as regards the offspring than alcoholism in the mother (Brühl-Kramer).

The results of recent researches into the specific effects of the liqueur called *absinthe* are very closely related to the varied symptomatology of alcoholic poisoning. This liqueur is generally admitted to be more used in France than anywhere else. Besides alcohol, it contains several ethereal oils (anise, fennel, etc.), of which the most important is the oil of wormwood. It has been over and over again observed in France that the disorders from which absinthe drinkers suffer differ from the customary forms of alcoholism by the frequency of well-marked epileptiform convulsions. Then Magnan[1] made experiments on animals with the different constituents of the absinthe liqueur, and found that moderate doses of oil of wormwood were sufficient to bring about paroxysmally occurring tetanic convulsions in dogs and other warm-blooded animals. Neither alcohol alone nor the other constituents of absinthe would do this in similar doses. Alcoholic mixtures containing the oil of wormwood produced the characteristic effects of alcohol in dogs, and a little later the specific effects of the wormwood.

The anatomical changes, in other words, the morbid anatomy of cases of chronic alcoholism is almost as protean and inconstant as the forms under which the disease occurs. We may find the most varied degenerations and atrophic conditions; and it is almost impossible to include all of them in this slight sketch. Of all the organs which are most commonly found diseased in the bodies of alcoholic patients, the mucous membrane of the gastro-intestinal tract takes the first place. There the

[1] Loc. cit. See also *Challand*, Étude expériment. et chimique sur l'absynthisme et l'alcoolisme. Paris. 1871.

various stages and sequelæ of chronic catarrh may be found, as has already been intimated.

According to Lancereaux[1] the thickening of the mucous membrane occurs especially in the stomach and cæcum; and is doubtless due to an overgrowth of connective tissue. On the mucous membrane of the stomach we find patches of hyperæmic vessels, sometimes flat (superficial) erosions, and very commonly indeed, a great increase in pigmentation. We do not know of any accurate microscopical researches on the changes in the glands of these organs.

No changes are to be met with in the organs of respiration which are specially characteristic of chronic alcoholic poisoning.

The large glands of the abdomen are far more frequently the seat of very extensive tissue-changes. The liver is sometimes found only exhibiting fatty degeneration, sometimes in the granulated condition due to interstitial development of increased connective tissue, which is, in fact, cirrhosis of the liver. The kidneys, though not quite so often, are affected in the same way.

As regards the nervous system and its envelopes (membranes), pachymeningitis hæmorrhagica plays so important a part, that it has been considered by many as pathognomonic of chronic alcoholism. According to Kreminansky (loc. cit.) and Neumann (loc. cit.) these changes can be induced experimentally by giving dogs alcohol for a long time, mixed with their food. The brain is sometimes attacked with a peculiar dry and tough condition, in which the cortical substance of the convolutions is smaller than usual (wasted), and the ganglionic cells have undergone fatty degeneration (Wilks[2]). Fatty degeneration of the voluntary muscles and the same disease of the heart, and thickening of the coats of the veins (pylephlebitis potatorum) till their calibre is almost obstructed, are very common conditions according to Lancereaux. The treatment of the different stages of alcoholic poisoning has given rise to a great deal of controversy and difference of opinion. In the acute form of alcoholic poisoning the stomach-pump has lately been used with very

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[1] Gazette hebdom. 1865.

[2] Journal of Med. Sciences. 1864.

good effect in order to remove the alcohol which remains in the stomach, often in large amounts. But for the rest, it may easily be understood that the chief part of the treatment must be purely according to the symptoms, since we possess no medicine which can act as a direct antidote to alcohol, or neutralize at once its pernicious effects. The local and general abstraction of blood, though formerly recommended, has very properly been generally abandoned. When coma threatens, and respiration is defective, cutaneous irritants (frictions, cold applications, mustard poultices, etc.), and under some circumstances artificial respiration, are indicated. Treatment by pouring in drugs, we believe to be superfluous and useless.

The therapeutics of delirium tremens, of late years, has chiefly consisted in the free use of *opium* in some cases, of the use of chloral in others, or the use of moderate quantities of alcohol—those authors who attribute the outbreak of delirium tremens chiefly to the sudden withdrawal of the alcohol express themselves most warmly as to the good effects of the treatment by alcohol (see Cuming, loc. cit.). Digitalis and the oxide of zinc have also been much recommended. It cannot, however, be denied that many cases of delirium tremens do very well without any special medication if the patients are carefully watched and nursed for a few days. Such treatment is indeed to be very highly commended in those cases where the general bodily condition of the patients is not such as to cause anxiety, and when the case is not complicated by any acute disease. The tolerance of those afflicted with this delirium for even enormous doses of opium is a well-recognized fact; and the opium treatment of the disease is one of the most widely-diffused methods. In estimating its success, it must not, however, be forgotten that in very many cases it seems to have no effect whatever on the progress and course of the disease. In those patients who are much reduced, and whose hearts show but little power, we consider the use of large doses of opium to be counterindicated. The points of view which appear to necessitate the use of narcotics coincide in this, that they aim at combating and overcoming the excitement and the sleeplessness. It seems, however, not to make very great difference whether opium, chloral, or some other

hypnotic be used for this purpose, if due regard be paid to the special points in the case and the constitution of the patient. An attempt to set up a model is just as objectionable here as anywhere else; and we do not think it by any means desirable to lay down as a canon that all cases of delirium tremens should be treated by large doses of opium. The recommendations of digitalis in delirium tremens, which have generally come from England or Sweden, have been based upon the most diametrically opposite views of the pathology of the disease and of the mode in which the drug acts. Fothergill[1] has very recently recommended digitalis, more particularly in those cases of delirium tremens in which the pulse is small and irregular and the propulsive power of the heart is weakened. But the ordinary condition of the digestive organs of tipplers is the chief objection to the general use of digitalis. Waring-Curan[2] has recommended *oxide of zinc*, in pills, as a tonic after-treatment. This ought never to be taken on an empty stomach. Those who have taken the zinc for a long time are said not to suffer from delirium tremens again, even if they return to excessive drinking. Marcet[3] has also observed good results from this remedy in cases of chronic alcoholism, and cured ten cases out of twenty-seven with it. Hermann (loc. cit.) says the acetate of zinc is the next best remedy to opium. But the general experience of the use of this remedy is not yet sufficiently large to enable us to give a decided opinion on its merits. The same may be said of the treatment by alcohol. It is very likely that many cases would do better by a more gradual withdrawal of the alcohol, or by allowing a little to be taken all through. Of the other remedies which have been proposed for delirium tremens, we may mention *capsicum*, which Hermann has several times used successfully when other means failed; also *camphor* and *sumbul-root*, which sometimes prove very useful to old topers; lastly, *tartar emetic* in large doses. Far more important than any, or all, of these remedies is the dietetic treatment of the patients, who, especially when the disease lasts long, require the diet to be carefully studied

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[1] Brit. Med. Journal. 1871.
[2] Lancet. 1868.
[3] Med. Times and Gazette. 1859.

and adapted to their case, in order that they may recruit their strength. The treatment of cases complicated by acute diseases belongs to the special departments of Pathology and Therapeutics.

The treatment of chronic alcoholism generally proves a failure, since we can seldom perfectly succeed in following the causal indication. In other words, we can seldom wean the patient from alcohol at a sufficiently early stage. Here, too, the proper nourishment of the patients is a subject of the greatest importance. We may say the same of the careful treatment of the stomach diseases from which they suffer. Nor is a moral régime suitable to the individual patient of less importance.

Drugs are of less value here than in delirium tremens. We therefore refrain from filling our pages with a long catalogue of remedies.

CHAPTER II.

POISONING BY CHLOROFORM.

It is scarcely possible to find any other substance except chloroform which combines, within so narrow a compass, properties at once so salutary and so deadly, as regards its action on the human body—properties, too, which, although exactly contrary, pass, by almost imperceptible gradations, one into the other. On this account, ever since Simpson introduced it into surgical practice in 1847, its action as a poison has engaged almost as much general attention as its therapeutic uses. And although it has again and again conquered in the now almost annual contest with new candidates for favor as anæsthetics, this very pre-eminence is doubtless due, in great part, to the diligent study which has been given to its dark side, and the precautionary measures these have suggested.

Chloroform (ЄHCl_3) is a very mobile colorless fluid, of greater density than water, not miscible with that liquid, and very volatile. When evaporated it should leave a peculiar but pleasant smell behind it, which some people characterize as "sweet," on account of the impression simultaneously made by the vapor

on the nerves of taste in the mouth, the sensations of smell and taste being curiously blended. Its physical properties render chloroform just as adapted to diffuse itself through the circulation, along with the inspired air, as it is unsuited for introduction into the stomach (by itself); for its sudden evaporation, and perhaps immediate action on the nerves of sensation, as a strong irritant to all mucous membranes, do not permit of large doses being introduced into the stomach for medicinal purposes. No doubt, however, some of the vapor gets into the blood, even when swallowed. Chloroform acts in a similar manner upon the skin, although its irritant action is less marked. It may pass into the blood through this channel also, provided the necessary external conditions are complied with (hindering its evaporation into the atmosphere, etc., etc.). This is rendered still more easy by the property chloroform has of easily dissolving the fatty matters which coat the epidermis of all parts of the surface, except perhaps the palms of the hands and soles of the feet—a property not shared by watery solutions. Parisot[1] has shown by experiment that when, for example, a solution of atropine in chloroform is applied to the skin, it is much more quickly absorbed than an alcoholic solution applied in a similar manner, its action being tested by the production of mydriasis.

The greater part of the chloroform is eliminated in the air breathed out of the lungs—that is, in expiration. But Perrin, Lallemand, and Duroy (loc. cit.) have found chloroform vapor in the cutaneous secretions of persons chloroformed, although they could not detect it in the urine.

Views and hypotheses founded upon *à priori* reasoning, on the well-known physical and chemical properties of this agent, have led to numerous mistakes as to its behavior in relation to the blood, and many errors had to be abandoned when they were put to the test of experiment.

For example, B. Clemenz thought that the rapidly fatal action of chloroform was due to its not containing any oxygen, because we cannot conceive of life with-

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[1] Sur le rôle de l'epiderme en presence de l'eau, du chloroforme, et de l'éther. Acad. des sciences. Séance du 17. VIII. 1863. Gazette des hôpitaux. 1863. No. 99. p. 396.

out oxygen. Others thought that chloroform sometimes rapidly abstracted oxygen from the blood, or decomposed it into prussic acid and sal ammoniac, etc. A more detailed account of these erroneous views may be found in the article by Schmiedeberg.[1]

But it was very soon established by the experiments of A. Boettcher (and, it would appear, simultaneously by Sansom[2]) that under certain conditions the blood of various animals is acted upon by chloroform in such a way that the blood-corpuscles are dissolved, and the hæmoglobin crystallizes out. In human blood chloroform produces the same solution, but no formation of crystals.

Schmiedeberg (loc. cit.) shows that it is highly probable that chloroform enters into chemical combination with the substance of the red blood-discs. For when defibrinated blood and chloroform are mixed together, outside of the body, there is produced a peculiar albuminous precipitate, of the color of red sealing-wax (chloroform coagulum), the chemical constitution of which shows a considerably greater percentage of chlorine than normal blood exhibits. On the other hand, the serum of the blood, mixed with chloroform, contains almost as much chlorine as normal serum. It would therefore appear that in this chloroform coagulum, from which very little chloroform can be recovered by simple distillation, this substance has entered into some peculiar combination with the blood-corpuscles, the exact nature of which we do not yet know. In the meanwhile the fluid portions appear not to contain any chloroform. It is a matter of great interest to note that in forming this compound chloroform loses its own peculiar and striking physical properties, so that, in medico-legal investigations on the presence of chloroform in the blood, it can never be recovered from that fluid except in extremely small (minimal) quantities.

Bonwetsch (loc. cit.) has also shown by his experiments that chloroform, like alcohol and ether, retards tissue-changes in the

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[1] Ueber die quantitative Bestimmung des Chloroforms im Blute und sein Verhalten gegen dasselbe. Archiv für physiologische Heilkunde. VIII. 1867.

[2] Ueber Blutkrystalle. Eine physiologisch chemische Abhandlung. Dorpat. 1862. Ueber die Wirkung des Chloroforms auf das Blut. Virchow's Archiv. XXXII. 1867. Chloroform, its Action and Administration. By *A. E. Sansom*. London. 1865.

blood. Blood mixed with chloroform gives up its oxygen (oxyhæmoglobin) to reducing agents far more slowly than normal blood.

Unfortunately, none of these facts are fully applicable to the living human body, since they all relate to blood drawn from the veins. No one has yet observed the blood-corpuscles, dissolved in blood, still circulating.[1]

Schmiedeberg (loc. cit.) thinks that it is very probable that the combination of chloroform with the blood-corpuscles which he has noted does not occur in the blood which circulates through a living animal, since the combination which occurs outside the body is again broken up by exposure to the oxygen of the atmosphere. The constant presence of oxygen in the circulating blood, therefore, renders it unlikely that any such compound can be formed in life. The conclusions drawn by Sansom[2] from the behavior of chloroform with blood are at least not to be implicitly relied on, since he does not hesitate to attribute the whole of the effects of chloroform to this solution of the corpuscles. We are still a long way off from a perfect knowledge of the effects of chloroform. Yet the facts just mentioned are valuable as furnishing us with hints (finger-posts) as to the direction our inquiries should take if we hope to succeed. That solution of the blood-corpuscles cannot well be the primary cause of the effects of chloroform would appear, amongst other reasons, from the fact furnished us by Hermann (loc. cit.), that even those members of the animal kingdom which have colorless blood are affected by chloroform. Some time since this observer laid especial stress on the effects of chloroform upon protagon, effects which he himself had demonstrated. These are common to all

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[1] *L. Hermann* (Ueber die Wirkungsweise einer Gruppe von Giften. Archiv für Anatomie, Physiologie, etc. 1866) remarks that a sure test of the occurrence of dissolution of blood-corpuscles is afforded by the presence of bile-pigments in the urine, and eventually by jaundice. We do not know of any further observations in this direction. Jaundice is sometimes met with as a consequence of chloroform narcosis, in accordance with Hermann's views.

[2] Loc. cit. p. 62. Narcotism (or, to speak more particularly, chloroform narcotism) is due not to a special poison which "mounts to the brain," but to the influence of an altered blood. "Narcotism is suspended oxygenation." (!)

the volatile anæsthetics. Protagon is the substance which O. Liebreich is admitted to have first discovered in the brain-substance. Volatile anæsthetics dissolve protagon, and this solution may probably be the basis of their anæsthetic operations, according to L. Hermann. It is quite out of the question for us to discuss here the question of the existence of protagon, or of its relations to lecithin. Under any circumstances we may pretty safely admit that these agents are solvents for those constituents of the nerve-substance which contain phosphorus. But alas! we are ignorant as to the part played by such substances in the vital actions of the nervous organs. Hermann's hypothesis is, therefore, as he himself admits, by no means one that fully explains the phenomena. But it is one of the best representatives of that class of theories which seeks to explain the operation of chloroform, not by any altered constitution or properties of the blood, but by a direct action upon the nervous organs. In the absence of fully explanatory facts, it is open to us to choose whichever of these theories we like, although we certainly believe that the opinion of a direct action upon the nerves is the most probable one.

The essential symptoms produced by chloroform are the expression of functional disturbances of the central organs of the nervous system. A short-lived exaltation of the activity of these organs is succeeded by a more or less perfect suspension of this activity; a suspension which, in extreme cases, extends to those centres of the vegetative functions of the organism (respiration and the action of the heart) which are usually not attacked. It is no doubt due to its physical properties that chloroform has the peculiar power of producing its narcotic effects, one after the other, in a far briefer space of time than is the case with most other narcotics. As quickly as it is received into the blood, and is again eliminated from it, so suddenly do its effects appear and disappear again. It has just been remarked that the action of chloroform is by no means limited in all cases to the organs which regulate the animal functions of life. And since this encroachment on the most important vital processes, those of respiration and the movements of the heart, are the special and almost only dangers of chloroform, it has for a long while been

the earnest endeavor of medical men to discover accurately the real causes which underlie these unwelcome properties. To this we owe a long series of careful experiments upon animals, which have been made with the object of discovering the causes of the toxic action of chloroform. Scheinesson[1] has explained the action of this poison on the circulation by means of experiments on animals. The movements of the heart become weaker, and the lateral pressure in the arterial system is lessened not only on this account, but because the vaso-motor centre in the spinal cord (or medulla oblongata) loses its irritability through the poison, and may even be perfectly paralyzed. The weakening of the activity of the heart does not depend upon any influence from the nerve-centres, but is dependent rather on a direct alteration of the motorial power of the heart, which may be considered by some as due to a weakening of the automatic centres for movement in the heart itself (ganglia of the heart), or on direct weakening of the muscular fibres of the heart. These changes in the circulation are, it would seem from Scheinesson's experiments, also the cause of the decrease in the bodily temperature, and of the retardation of tissue changes in chloroformed animals.

The results of the English *Chloroform Committee's* experiments perfectly agree with those of Scheinesson.[2] In these, also, decrease of arterial pressure was observed as a constant effect of chloroform. Lenz's[3] experiments with the hæmodromometer, in which the swiftness of the blood-current in the carotid artery sank to one-seventh of its normal value, also speak strongly of the diminished propulsive power of the heart from chloroform. Vierordt, however, established a far less considerable diminution of the rapidity of the circulation—amounting to about four-fifths of the normal rate. Brunner and Gall[4] have also made experiments upon the blood-pressure.

If we are thus able to refer the deaths from chloroform, in a large number of the cases, to the paralyzing effects of this agent

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[1] Untersuchungen über den Einfluss des Chloroforms auf die Wärmeverhältnisse des thierischen Organismus und den Kreislauf. Dissert. Dorpat. 1868.

[2] Report of the Committee appointed by the Royal Medical and Chirurgical Society, etc., etc. Med. Chirurgical Transactions. Vol. XLVII. 1864. pp. 323—412.

[3] Dissertat. Dorpat. 1853.

[4] Compare *Scheinesson*, l. c. p. 68.

upon the heart, it is no less true that there are yet other observations which make it more than probable that the fatal termination is sometimes brought about by paralysis of the respiratory centres.

Numerous experiments in this direction were instituted by the London Chloroform Committee. A difference was at once noticeable, according as concentrated or dilute vapors were inhaled. The duration of life of the animals (dogs) was almost directly proportional to the concentration of the vapor. The concentrations (or as we should call them, dilutions) used were (1) weaker, of air containing from 1 to 15 per cent. of chloroform; (2) stronger, with at least 40 per cent. of chloroform in the air. In the weaker compound, the intensity and quality of the symptoms produced were not much affected by the mode of breathing, whether through mouth or nose, or through an opening in the trachea. But when the strong concentrated vapors were used, through either mouth or nose, almost immediate slowing of the pulse (after 80 seconds), and respiration (after 105 seconds) occurred, and somewhat later, stoppage of the heart, in about five minutes. But if the concentrated vapors were inhaled through an opening in the trachea, the heart stopped before respiration ceased. The pulse always vanished a little before the movements of the heart ceased. Concentrated vapors often caused an immediate, though somewhat brief, stoppage of respiration. This was absent when a mixture of 6 per cent. of chloroform in air was employed. This was always followed by increased frequency of breathing, at first with greater, afterwards with less depth of the separate inspirations, which gradually decreased to nothing.

When diluted vapors were used, the respirations often sank to nothing, and then began again afresh after from twenty to forty seconds. The fresh application of chloroform stopped them again.

Section of the vagus nerve in chloroformed dogs had less effect than it has on dogs not under chloroform.

Chloroforming after section of the vagus nerve diminishes the consequences of this operation (increase of the frequency of the pulse and dyspnœa).

We must pass over a number of theories and experiments on the action of chloroform,[1] but we cannot refrain from alluding to one very important point as regards the true nature of chloroform narcosis. Some authors have considered the primary cause of the occurrence of certain symptoms affecting respiration and circulation to be a reflex irritation of the centres concerned.

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[1] Consult on this *Köhler*, Die neueren Arbeiten über die Anaesthetica. Schmidt's Jahrbücher. Bd. CXLII. p. 209, CXLV. p. 305, and CLI. p. 193.

Dogiel[1] and Holmgren[2] considered the stoppage of the heart and the disturbed respiration, which they both noted as common in animals in the first stage of the action of chloroform, as the result of a previous reflex irritation of the vagus centre in the medulla oblongata, through one of the sensory nerves of the nose, or of the naso-laryngeal mucous membrane. Holmgren (loc. cit.) has shown, however, that only those branches of the trigeminus are affected which ramify in the naso-laryngeal mucous membrane. The phenomena in question are weakened after section of the superior laryngeal nerves, and are altogether absent after cutting through the trigeminal nerves, as well as the vagus in the neck. These disorders are not produced in the first stage of the inhalation if the chloroform be inhaled through a tracheal fistula (thus avoiding the above-named portions of the mucous membrane).

Lastly, we must notice a view lately advocated by A. W. Smith.[3] This author considers that a very common cause of the stoppage of breathing in chloroform narcosis is to be found in the paresis (anæsthesia) of the termination of the sensory nerves in the lungs, induced by chloroform—these nerve-endings being concerned, in the normal state, with the regular performance of the respiratory movements. We cannot deny that there is some foundation for this theory, when we recall to mind the results of Breuer's[4] experiments on the part played by the peripheral terminations of the vagus nerves in the act of respiration. According to Breuer, each inspiration causes an irritation of the sensory terminations of the vagus nerve by the very act of expansion of the lungs. It is carried by the centripetal vagus fibres to the centre for expiration, and an expiratory movement is at once set up. By a similar mechanism an inspiration is made to follow an expiration, so that in a certain sense the movements of respiration are automatic and self-regulating. As the coöperation of the vagus

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[1] Ueber die Wirkung des Chloroforms auf den Organismus der Thiere. Archiv für Anatomie und Physiologie, etc. 1866.

[2] Virchow und Hirsch, Jahresbericht, etc. 1867. Referat von *Th. Husemann.*

[3] One of the Causes of Death from Chloroform. American Journal of Medical Sciences. 1871.

[4] Die Selbststeuerung der Athmung durch den Nervus vagus. Sitzungs-Bericht der Kaiserlichen Akademie zu Wien. Mathem.-physik. Cl. Bd. LVIII.

nerve plays a leading part in the whole of this mechanism, it is quite conceivable that the sudden paralysis of the sensibility of the lungs, especially when the central organs of respiration are simultaneously affected, must greatly contribute towards the stoppage of respiration. Richardson[1] believes that death from chloroform is brought about in many different ways, by functional disturbances of the various parts of the nerves belonging to or regulating the heart. We think, however, that his views are not much supported by fact, and are somewhat too dogmatic in tone. From the foregoing statements it is quite evident that our knowledge of the real nature of the action of chloroform is by no means sufficient to form data for precise theories and formal propositions. All the theories mentioned only correspond to certain special cases out of a great number of others, in a long series, whose combinations are often far from being manifest. The mania of many authors for the construction of positive and generally applicable propositions or theses as to the nature of the action of chloroform, and the original causes of death by chloroform, appears to us to originate in a faulty conception of the physiology of the subject.

Our present task is to treat of those circumstances in which experience teaches us that the unfavorable effects of chloroform are manifested, as if by preference; whilst we purposely neglect, for the reason assigned above, any further consideration of the primary physiological causes of death by chloroform. In our opinion, these causes have nothing to do with the etiology.

The cases of poisoning by chloroform which occur in medical practice are, for the most part, cases in which chloroform is made use of for surgical purposes. It is not always in the power of the surgeon, who seeks to utilize a part of the poisonous action of this agent, to exactly limit its operation, so as to shut out the unfavorable and unwished-for part of the same action.

In a smaller number of cases, latterly becoming more numerous, poisoning by chloroform occurs either to medical men, or to others who take it either for suicidal purposes or with the

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[1] On Death from Chloroform. Medical Times and Gazette. 1870, July 23, p. 85.

object of gaining sleep, which they have in vain sought to obtain by other means.

Lastly, we have lately met with cases in which chloroform, having been long taken as a sort of intoxicating agent (Genussmittel), for the pleasure it affords, has at last given rise to a kind of chronic poisoning. There are also a few cases of poisoning by chloroform which have originated in its being accidentally mistaken for some other fluid.

The statistics of death by chloroform in surgical operations have been very carefully collected by many observers for some few years past.[1] The numbers already collected relieve us from the necessity of discussing the question whether chloroform itself is really a cause of death, in spite of the well-known dictum of Sedillot, "Le chloroforme pur et bien employé ne tue jamais." The question, as to which stage of chloroform narcosis is most exposed to the danger of death, has been much and freely discussed. Apart from those rare cases in which the true cause of death must be sought, not in the chloroform used, but in what is called "shock," occurring after severe accidents, and sometimes occurring in very sensitive people—cases which ought properly to be excluded from our consideration—we shall be very nearly right if we admit, with Billroth, that death may occur in all stages of narcosis. But the statistical material at our disposal does not allow us to draw any absolute conclusions from it, as regards this point.

The following figures are taken from Sansom[2] and the Report of the Chloroform Committee.[3] The first author gives the following table:

Stage of the Operation in which Death occurred.	Author.		
	Snow.	Scoutteten.	Kidd.
Before the operation began	18	22	14
During the operation	22	6	14
Soon after the operation	6	12	7

[1] It appears to us quite unnecessary to consider in any detail the now celebrated controversy as to the relative merits of ether and chloroform. It is very likely already decided, whilst we write this, in favor of chloroform [—not in America; see foot-note, p. 443].

[2] Loc. cit. p. 65.

[3] Loc. cit. p. 374.

The Chloroform Committee collected 109 cases, of which there died:

At the beginning of the inhalation	10
In the stage of excitement	16
Under imperfect anæsthesia	24
With perfect chloroform narcosis	38
After the operation was over	14
Not known at what period	7
	109

or,

Before they were perfectly under chloroform	50
During chloroform narcosis	52
Condition not known	7
	109

The fact, first specially noticed by English authors, that an overwhelming majority of the fatal cases are in males, is very remarkable. The proportion between men and women, according to the statistical materials furnished us by Sansom,[1] is as follows:

According to Snow	3 males	to	2 females.
" Scoutteten	2	"	1 female.
" Kidd	4	"	1 "
" Sansom	2.8	"	1 "
" Committee	72	"	37 females.

Sansom justly remarks that this result is all the more remarkable, inasmuch as the obstetric use of chloroform in childbirth has given women almost a monopoly in its use.

The age of the individual does not seem to have any special influence. That very young children bear chloroform extremely well, as a rule, is evident from the hare-lip operations one so often sees [and from the experience of ophthalmic hospitals, notably Moorfields.—Trans.]. It would, however, be rash to decide on these grounds that children under five years of age possess an absolute immunity from the ill effects of chloroform. Indeed, there have been cases observed of late which show the contrary result, and perfectly justify Bouvier's[2] caution to neglect none of the usual precautions, when administering chloroform to small children.

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[1] Loc. cit. p. 67.

[2] Bulletin de Thérapeutique. Aug. 1867.

The statistics of the Chloroform Committee (and we have as yet no others which we can trust) only show that most chloroform deaths occur precisely in those periods of life in which the greatest number of men are chloroformed.

Under	5 years	there died			0
From	5–15	"	"	"	9
"	15–30	"	"	"	30
"	30–45	"	"	"	32
"	45–60	"	"	"	12
Over	60	"	"	"	2
At unknown ages		"		"	24
					109

Constitution and physical strength seem to stand in this peculiar relation to chloroform, that robust and healthy systems seem far more exposed to the dangerous effects of this material than delicate, weakly men who have been reduced by previous ill-health. Sansom[1] discovers in this a certain "law of tolerance." As a result of this law, chloroform is far less dangerous for women and children than for men. We may also explain in a similar way the fact that the largest relative number of fatal cases of chloroform administration have occurred in cases of very trifling surgical operations, minor cases, such as the extraction of teeth, the operation for removal of ingrowing nail, and such like, where for the most part the general health of the patients has been tolerably good.

Sansom collected 107 cases of death from chloroform, in which the reasons for which it was given are assigned, and from these it appears that

I.	After very slight operations there died	62
II.	" more severe " " "	26
III.	" "capital" " (amputations, lithotomy, etc.) there died	7
IV.	" herniotomy, forceps-labors, there died	6[2]
V.	Delirium tremens and mania, there died	4
VI.	Natural labor, there died	2
		107

[1] Loc. cit. p. 68.

[2] [In my copy this reads "Reduction of dislocations (5); forcible extension, 6." Instrumental labors go in class II., and herniotomy in class III.—Trans.]

Our space does not allow us to enter at greater length into Sansom's arguments on this point. An objection may fairly be raised that the total number of cases collected is not sufficient to allow of safe conclusions. And again, it may be said that minor operations are far more common than more severe ones, and must therefore, in the nature of things, furnish a larger number of fatal cases. For these reasons it is perhaps well not to lay too much stress on the "catholicity" of the "principle of tolerance."

It is not possible to say exactly how much chloroform can be given to any one without danger to life, because it is in most cases quite impossible to accurately estimate between the quantity of chloroform used and that actually inhaled, or, in other words, absorbed (resorbirt). However, all authorities agree in this, that the degree of concentration of the chloroform vapor, the more or less perfect absence of atmospheric air in the respiratory medium, is of special importance. That concentrated vapors can destroy animal life in an exceedingly short space of time has been many times demonstrated by actual experiments; surgical experience leads to the same conclusion.

On the other hand, the actual quantity of chloroform inhaled, if spread over a longer space of time, is of less importance, and Sansom[1] calls attention to the fact that death very commonly occurs after only a few whiffs of the chloroform, and much more rarely in the later stages of narcosis. The figures given by the Chloroform Committee can scarcely be said to confirm this. Our own view is, that on this point also we must suspend our judgment. This much is, however, thoroughly established by cases, that very large quantities of chloroform may be inhaled safely enough, whilst very frequently quantities which are very moderate indeed may bring about fatal accidents.[2]

It is almost equally difficult to determine what is a fatal dose of chloroform, when taken into the mouth, and swallowed as a liquid. In six cases of this sort which ended fatally, from one-half to eight and a half fluidrachms of pure chloroform were taken. Ever since chloroform has been popularized in surgical

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[1] Loc. cit. p. 73.

[2] It is scarcely necessary to dilate upon what is called "idiosyncrasy" with regard to chloroform as a primary cause of its injurious effects.

practice, the general experience of medical men has confirmed their belief that certain morbid states of the system are particularly liable to danger from chloroform narcosis.

Amongst these special prominence must be given to anomalous conditions of the heart. Here, too, we must admit that in many cases "post hoc, ergo propter hoc," has led to erroneous conclusions. Sansom[1] insists, and rightly so, we think, that simple valvular incompetency, in the absence of fatty degeneration of the cardiac muscles, does not render chloroform more dangerous, or contraindicate its use. This opinion has been amply corroborated by practical experience. But unfortunately the one pathological condition of the heart which seems to be really a predisposing cause of the bad effects of the narcosis—fatty degeneration of the cardiac muscles—is, as a rule, diagnosed first on the post-mortem table.

Indeed, as regards this, we can scarcely talk of clinical experience, as Koehler does (loc. cit. 2. Article. p. 25). Indeed, no case is known to have been chloroformed in spite of a previous diagnosis of "fatty heart," and then, after death, this condition to have been found. But this is what we should understand, when we are told of clinical experience being confirmed. That 21 out of 55 cases exhibited fatty hearts when examined post-mortem is just as much to the point as Kidd's experience, that, in 250 cases of sudden death, he never found a single case of degeneration of the heart. Whenever it is possible to diagnose this condition with absolute certainty, we shall hold clinical observers inexcusable, if they exhibit chloroform in such cases. But at present the fact that chloroform is injurious in fatty degeneration of the heart is a result, not of clinical experience, but of post-mortem pathology.

Sansom (loc. cit., p. 76) has collected 55 post-mortem records of fatal cases of chloroform, with special reference to the condition of the heart. In 21 cases the heart was perfectly normal; there was fatty degeneration in 18; in 14 it was pale, soft and flabby; and in two cases there was valvular incompetency. No one as yet has actually proved that the cardiac changes in any case have been the primary cause of the death from chloroform.

There is also a general agreement amongst authors, as to this, that alcoholism may greatly increase the dangers of chloroform narcosis. This has been observed not only in the cases where chloroform has been given to calm the excitement of delirium

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[1] Loc. cit. p. 77.

tremens, but also in surgical operations on drinkers, in whom chloroform narcosis is generally very difficult to induce, and runs an irregular and unfavorable course. Kidd (loc. cit.) has collected nine cases in which chloroform, used as a remedy in delirium tremens, proved fatal; and Sansom (loc. cit.) has brought together eight other cases in which chloroform, administered to habitual drinkers for surgical operations, ended fatally. Without disputing that alcoholism may serve as a predisposing cause of death from chloroform, we must add that it is not safe to assume that all these cases really died on this account. For, whenever a death occurs from chloroform, we can easily understand that every effort will be made to remove a part, at least, of the blame from the chloroform itself, and the mode in which it was administered, and thus undue significance may be given to such conditions as the one named. Our experience has furnished us with cases enough in which regular sots, who exhibited great resistance to the effects of chloroform, have inhaled great quantities without a trace of injury from it.

English authors (Snow, Sansom, and the Report of the Chloroform Committee) lay great stress on the different methods and modifications of inhalation, as regards the amount of danger. But in regard to this the real point of importance is the concentration of the vapor and the amount of admixture of atmospheric air. Let the circumstances be what they may, the most dangerous of all methods is the administration of chloroform to one's self.

We must now sketch briefly the symptoms of chloroform narcosis in its various stages, and the effects of chloroform in human beings.

The first subjective symptoms, which are noticed almost immediately when chloroform is brought close to a patient, are a burning feeling in the nose and conjunctiva and a remarkably sweet taste in the mouth. Tears and saliva are generally secreted more abundantly, and the latter most generally causes efforts to swallow, which frequently bring considerable quantities of chloroform, in the gaseous form, into the stomach, which may at once induce vomiting.

If the air charged with chloroform be now breathed continu-

ously for some little time, we get in different individuals a number of symptoms, which are as multiform, indefinite, and varying as the psychical conditions of the individuals; they defy any precise description or analysis. All we can do is to describe some of the chief characteristics, and point to some of the varieties brought about by individuality and external conditions.

In most of those who are chloroformed, there is observed during the so-called first stage, or stage of excitement, a striking alteration in behavior and in the expression of their feelings. Most commonly this change of feeling is a cheerful one, manifested by laughing, gay gestures, singing, etc., but it is not rare to find the patient melancholy, weeping and wailing, and sometimes very angry, and there may sometimes be temporary mania. It is impossible to say on what this behavior depends, or why it assumes such different aspects in different cases. People who are usually cheerful become lachrymose, mild people get angry, modest and retiring people get bold and shameless, and *vice versa*, in manifold and complex variety. Just in the same way, under the influence of chloroform narcosis, the patient's character alternates from grave to gay, from lively to severe. It is, indeed, indisputable that this condition strongly resembles the slighter degrees of alcoholic intoxication.

Those who divide chloroform narcosis into several clearly defined stages do, in fact, prefer method to truth. Their picture is clearly drawn, and its colors are bright, but it is not like nature! For example, even the first stage, which we have been trying to sketch, is very different in different people, if we investigate the amount of consciousness, the degree of mental activity and of sensibility, etc. As a rule, the senses are not much affected in the very beginning. But their activity is very soon affected. Those who are chloroformed very soon become conscious that their senses are rendered more acute—there is a peculiar sharpness about them, a vast increase in the force of particular sensations; for example, the ticking of a watch seems like strokes of a sledge-hammer; not infrequently the words that bystanders whisper gently are heard with amazing distinctness. Other senses besides hearing are sometimes, but less commonly, inten-

sified in a similar way. The sense of sight, as a rule, is affected in an exactly contrary manner—a cloud seems to come over the eyes, and prevents the objects around from being seen clearly, and at last things seem to be all jumbled up together. Taste very soon becomes as it were lost, and at last all the senses become more or less impaired and defective. As a rule, consciousness remains intact during this first stage, although necessarily affected by the false coloring of the anomalous sensations we have described. The reflective faculties are therefore unimpaired, so that questions are answered correctly. Indeed, there are many men who give correct answers during this stage as regards their sensations. But many others are so altered as to be quite oblivious of those around them, or of the circumstances in which they are. In their condition of half-awake and half-asleep, they busy themselves with the past, "wear their heart upon their sleeve," and declaim loudly like those under delusions, or as if they were dreaming aloud; they sing and pray as though they were in church, and answer incorrectly, or not at all, when they are questioned. Lastly, although such cases are rare, we meet with those who, after inhaling a few whiffs of chloroform, fall rapidly into a deep slumber, without any trace of a preliminary stage of excitement. The objective symptoms of this first stage are, as a rule, exceedingly well marked. The face is flushed, the forehead bedewed with perspiration, the pupils are manifestly contracted, and the body makes either definite, voluntary, and well-co-ordinated movements (tries to rise up, walk, hit out, etc.), or is moved spasmodically (generally with extreme tension of muscles) hither and thither with no apparent object. Hiccups and vomiting often set in, the pulse seems somewhat quickened, and its resistance in general diminished.

During this stage sensation, too, is by no means uniformly affected. Many patients complain of crawling sensations (formication), like insects crawling over them, felt in the extremities, and unpleasant feelings of pricking and stinging in the skin—symptoms which are generally associated even then with diminished sensibility to external irritants. Partial or complete anæsthesia of the skin has frequently been observed even in this early stage.

The duration of this stage of excitement seems to be subject to no rule, and the limits of variation are very wide, and do not seem at all definite. If the inhalation be vigorously pushed, it is commonly found that a very few minutes suffice to change the scene. The previous excitement is either suddenly or more gradually allayed; the talking, singing, swearing, and so forth, is hushed, the muscles become relaxed and limp, the arms are dropped, the flush on the face vanishes, and deep sleep is indicated by very audible snoring.

The relaxation of the muscles very soon extends all over the body. The masseter muscles perhaps resist the longest. Breathing is deep and slow, as in those who sleep; the movements of the heart are somewhat weakened, but still regular. The pupils now become some whatdilated, and when narcosis is quite complete the ball of the eye can be touched without exciting any reflex movements of the eyelids; there is, in fact, perfect anæsthesia, and we may now use the surgical saw or the knife or the actual cautery without the patient being at all conscious of it, and without exciting any reflex movements. The general rule seems to be that sensibility lingers longest in the region of the sensory branches of the trigeminal (fifth) nerve, at the tip of the nose, and in the two temporal regions. The lower limbs and other parts of the body may be quite insensible to pain, whilst the corneal conjunctiva still gives rise, when touched, to active movements of a reflex nature. It is therefore quite unnecessary in surgical operations to delay the beginning of the operation till such time as the eyeball becomes insensible.

If the chloroform be pushed still further, it is very easy to reach a third and very undesirable stage, in which death occurs, for the most part, very suddenly, sometimes under the guise of syncope, sometimes taking the form of asphyxia. Herein lies the special risk of chloroform, that danger comes before it is expected, and that what we call unfavorable or dangerous symptoms are generally the immediate forerunners of death. In fact, death treads on the heel of danger. A sudden stoppage of the pulse or breathing, a sudden paleness overspreading the face, cyanosis or duskiness of the lips and dilatation of the pupils, and sometimes sudden relaxation of the sphincters, the passage

of urine and fæces, vomiting, a sudden stoppage of the flow of blood during an operation—these are the alarm-signals; and of these sometimes one, sometimes another, most prominently attracts the attention of the by-standers. We have previously discussed the physiological questions concerned in this condition. We need only repeat here, that it is by no means easy to say, in any given case, whether cardiac paralysis (syncope) or the respiratory centre has brought about the unfortunate ending. We may grant that the first method is the commoner one, and at the same time the more quickly fatal one, since attempts at resuscitation are generally quite useless; whilst anomalies of respiration, conditions of apnœa, or mechanical obstruction to breathing, in consequence of paralysis of the tongue and of its falling back and obstructing the aperture of the glottis, and similar conditions, can generally be remedied by appropriate means. In the first class of cases the face, as a rule, grows pale, and we note a stoppage or irregularity of the pulse, whilst respiration continues a little longer; in the latter class of cases, the various disturbances of respiration and the interruption of the breathing precede the stoppage of the pulse. Death is not seldom quite sudden. Violent cramp-like muscular movements must also be regarded as an unfavorable symptom, which commonly ends with the patient's dying suddenly. Sansom (loc. cit. p. 92) remarks that this is particularly likely to occur in those patients who have tippled freely, and in whom it is very difficult to induce narcosis.

We have previously insisted that we can as yet give no precise rule as to which stage of chloroform narcosis is the most dangerous. Indeed, there are not wanting authors who insist that the unfortunate cases are more apt to occur at the very beginning of the chloroforming (often, indeed, after only a whiff or two of it) than they are in the later stages.

We now return to the cases in which the desired narcosis is obtained without any untoward complications. If the inhalation be discontinued, the narcotized patient generally awakes suddenly, as from a deep sleep, in from one-half to three-quarters of an hour, without the faintest knowledge of what has befallen him in the interval. After some slight delirium and confusion,

the senses gradually return. Vomiting often occurs in these cases, but there is seldom any other abnormity. Serious sequelæ are hardly ever known to occur. In rare cases, however, the course of the narcosis is so far abnormal as to be complicated by general convulsions, of varying severity. These convulsions, which are sometimes epileptiform, and sometimes of a tetanic nature, may sometimes be sources of considerable danger, in so far as they involve more or less deeply the muscles of respiration. The real nature and cause of these convulsions is at present simply conjectural.

We must briefly consider those cases which are remarkable, either for the unusually long duration of the narcosis, or for the persistence, when the narcosis is over, of certain anomalies of the nervous system, such as anæsthesias, paralyses, and the like, for more or less time. All these modifications point to individual peculiarities in the constitution of the nerve-centres, and have been noticed to occur occasionally as after-effects of most narcotic poisons.

Although the published cases have been recorded less accurately than we could wish, it is no longer possible to deny the existence of a peculiar *chronic form of poisoning* or *intoxication by chloroform* (chloroform drunkenness). For the most part this consists in the ordinary use or abuse of large quantities of this narcotic, which is first employed for therapeutic purposes (the relief of pain, or to procure sleep, etc.), and gradually becomes an almost absolute necessity to the morbidly altered nervous system, as is the case, although in still more marked a manner, with alcohol and opium.

The cases of this kind observed up to the present time present symptoms of mental (or psychical) alienation, and are more particularly of the class denominated periodic psychoses, to which the abuse of chloroform seems to predispose.

This was at all events unmistakably evident in a case which fell under our own observation. Perfectly free and lucid intervals alternated in this case with attacks of the most intense melancholy and delusions as to persecution, leading to several attempts at self-destruction. No chloroform was consumed in the free intervals. Büchner's case (Husemann, loc. cit. p. 682) also took the form of periodic mania. Two other cases by Merie (loc. cit.) and Vigla (Med. Times, Nov. 21, 1855), in the first of which about a pound every five days, in the latter from twelve to fourteen drachms daily of chloroform were used, were, it would seem, of a different kind.

Merie's case appeared to e one of extreme moral depravity, a sort of moral insanity. The patient, who had formerly taken morphia, gradually became unable to procure sleep in this way, and so betook himself to chloroform. He laid in bed nearly all day, and chloroformed himself whenever he woke. At last he accidentally fractured both thighs; these had to be amputated, and this was done under chloroform, which acted very nicely for this purpose. He finally sank with symptoms of general marasmus. In Vigla's case there was also a peculiar kind of insanity.

It appears by no means an unusual thing for people who thus intoxicate themselves with chloroform to begin with inhaling it only, and to go on to take it internally. This naturally leads us to make some brief remarks on the way in which chloroform affects the stomach. As regards this, our present information is by no means copious. The report of the Chloroform Committee (loc. cit.) contains four fatal cases, Tardieu's work on poisons,[1] three each of death and of recovery. Out of ten cases in all, seven ended fatally. The narcotic symptoms in these cases are, from obvious reasons, complicated by the local gastric affection, consisting in the vomiting of quantities of slimy, and sometimes bloody, matters, and of violent epigastric pains, etc. Simultaneously, it is usual to find the narcotic operation of the poison fully developed, and in several of the cases the poisoned patient has been found in a condition of the deepest coma, with dilated and immobile pupils, deadly coldness of the extremities, and almost imperceptible pulse. Death is sometimes preceded by convulsions.

The post-mortem appearances in those who die comatose from chloroform do not afford a single characteristic or pathognomonic sign. Whatever may have been set down as characteristic in the past, we now know is to be met with in many other kinds of death. We shall therefore waste no time in the discussion of this question. In cases where this poison is taken by the mouth, it is easy to understand that we shall find more or less severe lesions of the mucous membrane of the gastro-intestinal tract—sometimes only simple reddening, sometimes ecchymoses and signs of extensive and severe inflammation.

The *prophylaxis*, or, in other words, the cautious application

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[1] Étude médico-légale et clinique sur l'empoisonnement. Paris. 1867.

of this narcotic, is the most practical and important part of the whole question. We cannot enter here on a detailed consideration of the principles on which the administration of chloroform (with safety) is founded. This is a subject which partly belongs to surgery, and partly to materia medica. An anxious and painstaking observation of both pulse and respirations, as well as of the external appearance and behavior of the patient under chloroform, with especial reference to those symptoms which we have spoken of before as indicating danger, should always, when chloroform is administered, be the special duty of an assistant skilled in this matter, who should have nothing else to do but to superintend the narcosis. In other words, whoever is giving chloroform should have nothing else to do but watch its effects and administration.

A sufficient amount of atmospheric air mixed with the chloroform all the while it is administered is indeed the chief element of safety. The moment any threatening symptoms are noticed, the chloroform must of course be immediately suspended. The proper *treatment* of poisoning by chloroform will, therefore, necessarily depend on either combating the tendency to death from cardiac paralysis, or on striving to recall the patient from a condition of asphyxia. In practice, however, these two objects are not so remote as they may seem to be in theory, since, as a rule, the cases in which there is any considerable risk from symptoms of cardiac paralysis are cases in which also the business of respiration comes to a standstill. The practical significance of the distinction is lost if we reflect that the means of deliverance in both cases are very nearly identical.

Widely as authors differ as to the mode in which death occurs in poisoning by chloroform, they all, with very few exceptions, agree in earnestly recommending that we should immediately and energically set about artificial respiration in all cases of threatened death from chloroform. Those who contend for the toxæmic theory, which attributes the injurious effects of chloroform to the action of this agent in robbing the blood of its oxygen, make oxygen play the principal part in their therapeutic efforts, and some have recommended the inhalation of pure oxygen gas (Blanchet, Jackson, Ozanam, etc.). Those who, on

the contrary, regard chloroform as a direct nervine poison (Lallemand, Perrin, and Duroy), admit the advantages of this means of treatment, since the poison still present in the blood and nervous system may thus be taken into combination, although its elimination is hindered by the paresis of respiration. They even think that inhalations of nitrogen or hydrogen might be useful in this way. Another group of authors, whose views are intermediate between those named above, and who consider its action on the cardiac nerves and the muscular fibres of the heart as the real element of danger, still consider that in oxygen we have a salutary irritant, which may spur on or rouse up the heart, which has in one or other of these ways been paralyzed, to new activity. All these theoretical views appear to us unsatisfactory and crude.

Let us be content, for the present, to establish this proposition, that in all cases where the natural respiration is deficient or wanting, we ought at once to set about artificial respiration. How far we act upon the heart and its movements in this way we cannot as yet determine. Nor need we enter into details as to the best way of instituting and carrying on artificial respiration. The proposal of C. O. Weber, to act upon the phrenic nerves in the neck by faradization with a fork-like electrode, simultaneously applying one electrode to the diaphragm, seems to us one of the most useful. It is warmly commended by Weber.

Simple inflation of air and passive artificial respiration by up-and-down movements of the thorax, drawing the tongue forward at the same time with a pair of forceps, have been successful in many cases. If the heart has actually stopped beating, direct electro-puncture of the heart has been several times proposed, and carried out. It certainly deserves a trial in any case, and should be combined with artificial respiration. But we have not much reliable experience on this point, and besides, we cannot assume that the results obtained by experiments on animals will also follow in the case of human beings. When threatening symptoms in chloroform narcosis have been marked by sudden collapse, pallor, apnœa, etc., it has generally been customary to apply strong irritants to the skin, in order to rouse the par-

alyzed nervous system, and to stimulate it to its usual reflex action—of course combined with artificial respiration. Pouring or sprinkling of water, dropping ether on the skin, the application of strong water of ammonia to the mucous membrane of the throat, all belong to this category. Sansom (loc. cit.) has lately opposed this sort of treatment, and especially recommended warmth as a means of resuscitation, combined with artificial respiration. But at the proper time—that is, immediately on the first indications of collapse setting in (small pulse, pale face, etc.)—the application of these means, or the mere sprinkling of cold water, does most undoubtedly have a good effect.

There is no medicinal treatment for cases of chloroform poisoning, because we know of no direct antidote to chloroform. Cases of poisoning by the internal administration of chloroform must be treated on general principles.[1]

CHAPTER III.

POISONING BY ETHER (SULPHURIC ETHER—DI-ETHYL ETHER—ÆTHER SULPHURICUS).

Ether, which is a colorless and extremely mobile fluid ($\Theta_4H_{10}\Theta$) has a very much lower boiling point than chloroform. The latter boils at 62° C. = 143.6° F., whilst ether boils at only 35° C. = 95° F. It is also of much less specific gravity than either chloroform or water, very volatile, and the vapor diffuses a very intense characteristic odor, which can be recognized clearly when very much diluted. Ether does not mix with water, but it is miscible with alcohol in all proportions.

Like chloroform, ether can gain access in a gaseous form to the blood, through the surface of the organs of respiration, both in human beings and in other animals.

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[1] In a case of this kind, where an old man had swallowed nearly one ounce and a half of chloroform, I administered oil, and then solution of sulphate of zinc with the stomach-pump, afterwards demulcents and stimulants per rectum. He recovered.—TRANS.

Absorption from the mucous and serous membranes takes place more slowly. It has been found, when it is introduced into the stomach, rectum, or serous cavities, that very much larger quantities of ether are required to produce its characteristic effects than when it is inhaled. Anstie[1] strives to explain this in the following way: When it is introduced through mucous or serous membranes, the ether which is absorbed must necessarily pass through the portal system of veins and the lesser circulation, before it can get into the arteries, and thus reach the seat of its operations. From this we may infer that small quantities of ether may be discharged from the lungs before any effect on the general system is produced. Indeed, the elimination of ether by the lungs has been repeatedly determined by experiments (Snow, Anstie, Lallemand, etc.); it has also been found in urine, though in very small quantities. In this way it has been established that a very large quantity of the ether which is taken in leaves the body in the same form, quite unchanged. Whether the remainder is decomposed in the body is as yet unknown. The effects of ether on the blood are essentially the same as those already mentioned when discussing chloroform, with the exception of the peculiar compound described by Schmiedeberg (loc. cit.), as occurring between one constituent of the blood and chloroform. No similar compound has been described as occurring with ether. Like chloroform and alcohol, the effect of ether on blood is to retard the giving up of its oxygen to reducing agents (Bonwetsch, loc. cit.). The blood of etherized animals has a remarkably dark, venous appearance. The effects of ether are partly due to its remarkable rapidity of evaporation, producing a fall of temperature, and partly to a peculiar and as yet unexplained property possessed by ether of acting as an irritant on the terminations of the sensory nerves in human beings. Since ether boils at (or even below) the temperature of the body, there is this danger when introducing large quantities of fluid ether into the stomach, that through the expansion of its vapor the intestines may be so greatly distended that the respiratory movements of the diaphragm may be thus rendered impossible.

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[1] Stimulants and Narcotics. London. 1864.

Claude Bernard[1] has shown that the functions of secreting organs are rendered more active by ether when this substance is applied in or near the locality of their excretory ducts. For example, the gastric juice, the pancreatic juice, saliva, etc., are much increased in quantity when it is given internally to animals. Glycosuria is very commonly, though not constantly, produced by ether ; whether we consider, with Claude Bernard, that this symptom is also to be regarded as a phenomenon of irritation, and as the expression of an increased secretory activity of the liver, or whether, with Anstie, we should regard it as a sign of weakened functions, a sort of paralysis or narcosis of the liver, we will not attempt to decide. In any case, the production of diabetes by ether must be classed along with the other forms of diabetes due to the action of poisons, regarding which we unfortunately as yet know very little. Although the other local effects of ether are of little interest from a toxicological point of view, the general effects of this substance agree in most points with those of chloroform and other anæsthetics. Here, too, we must regard them as essentially due to the general operation of a change in the functions of the nerve-centres, of the exact nature of which our present knowledge is extremely limited. Here, too, an exalted sensibility of individual nerve-centres precedes the more or less perfect suspension of consciousness, and the loss of the knowledge of things external to the patient.

The long-discussed, and as yet unsettled question, as to whether ether or chloroform is best fitted for the production of surgical anæsthesias and for other therapeutic purposes, or which is the safer of the two, has instigated numerous experiments on the physiological effects of ether. There is a pretty general agreement that large quantities of ether are required for the production of perfect anæsthesia. The chief difference between ether and chloroform seems to be the opinion advanced by most of the experimenters as to the relation of ether to the activity of the heart. Whilst chloroform admittedly kills in not a few instances by bringing about a stoppage of the heart, ether almost always proves fatal by paralyzing the respiratory

[1] Leçons sur les effets, etc. loc. cit.

centres. Anstie (loc. cit.) lays special stress on the way in which ether affects the sympathetic nerves—which is shown by the reddening of the face, the breaking out of perspiration, increased secretion of saliva, and increase in the frequency of the pulse. Unfortunately, there are as yet no conclusive experiments in this direction, so as to set the question at rest whether these phenomena do really depend upon the implication of the sympathetic nerve.

As regards the order in which the functions of various parts of the nervous system are affected, or one may say abrogated, by ether, Flourens[1] and Snow[2] state that, in the first instance, the peripheral sensibility and the co-ordination of the voluntary muscles are affected and abolished, and in such a manner that sensibility in parts at a distance from the brain and spinal cord lose sensation earlier than organs which lie nearer to these. Then follows suspension of consciousness, and last of all, the breathing is suspended. The movements of the heart go on some time after respiration has ceased. Valuable as all this may be from a practical point of view, it is yet clear that we are still in want of more definite knowledge, to enable us to draw any very accurate distinctions or conclusions between these different anæsthetics and their operation.

The etiology of ether poisoning differs only very slightly from that of poisoning by chloroform.

Most of the cases occur from its medicinal or surgical use in those places where it is preferred to chloroform. Besides this, the internal use of ether (Hoffmann's anodyne) may lead to poisoning. It must also not be forgotten that in some countries (north of Ireland) ether is taken as a sort of luxury, to induce narcosis; and it is very easy to understand that poisoning cases may occur in this way.

In spite of all this, the published cases of poisoning by ether are very few, and bear no comparison at all with the numbers of cases of poisoning by chloroform. However, this is not so much due to the greater safety of ether, but rather to the fact that whilst the use of ether has steadily diminished, that of chloro-

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[1] Compt. rend. XXIV.

[2] Chloroform, etc. loc. cit.

form has as constantly increased. [We doubt if this be true of the last two or three years in the British Islands.—TRANS.] [1]

Neither the poisonous nor the fatal dose of ether has yet been determined, and we therefore refrain from giving figures which can only be founded on isolated cases. At least half an ounce of ether is required to fully anæsthetize a grown-up person, and, as a rule, considerably more. Just as it is with chloroform, so is the case with ether: the degree of concentration of the vapor and the amount of atmospheric air mixed with it are the chief matters of moment.

The symptoms of ether narcosis are pretty well known, partly from observations on patients, and partly from the experiments of those who have taken it themselves (Anstie). All agree in giving prominence to the unpleasant odor of ether, which is probably one of the chief obstacles to its general use as an anæsthetic. The first symptoms verified by Anstie in several experiments upon himself were a general feeling of exhilaration of spirits, with an inclination to laugh, a pleasant feeling of warmth, extending all over the body, and palpitation of the heart, with increased frequency of pulse. This is soon succeeded by a feeling of numbness and pricking sensations, commencing with the lower extremities, quickly running all over the body, with a breaking out of perspiration on the forehead. Surrounding objects began to dance before his eyes; he was unable to control or verify the movements of his hands, and felt as if there were enormous weights on all his limbs. Then he lost consciousness. From the observations made by him it would seem that he lost the power of writing as early as about forty seconds after the beginning of the inhalation, and that the narcosis from inhal-

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[1] The enormous clinical experience with ether in America (seemingly unknown to German authors) overwhelmingly disproves the inference above made. There is no escape from the conviction that ether kills so seldom, simply because it is so safe. As admitted by the author, ether almost never primarily paralyzes the heart, and its only dangerous effect—stoppage of respiration—is one easily foreseen by striking premonitory symptoms, and readily and surely relieved by the simple means of removing the anæsthetic and making a few passes of artificial respiration. New York surgeons, thus convinced of the vastly greater safety of ether, very generally prefer it to chloroform, and the same is probably true of the majority of American practitioners.—EDW. CURTIS.

ing half an ounce of ether had lasted thirty-five minutes before he again recovered consciousness. When he first recovered consciousness he felt unable to move, and had a feeling of crawling (like insects creeping) in the limbs ; in a few minutes more, however, he felt perfectly himself again.

In other cases, a great degree of motorial excitement has been observed in the first stage of the operation of ether, along with unconnected speech, laughing and crying, just as is often observed in narcosis from chloroform. The flushing of the face, the occurrence of sweating, the increased frequency of the pulse, are matters on which most authors are agreed.

In cases which have ended fatally, there has usually been noticed a sudden stoppage of the breathing, which is, as a rule, not much affected in the ordinary cases. But stertorous breathing has sometimes preceded death. Convulsions have not been observed in these cases.

The pupils, which have either been contracted or unaltered during the normal narcosis, have suddenly dilated at the moment of death.

Martin[1] has recorded a case of chronic poisoning by ether in a woman who took large quantities of ether (internally) on account of pains in the stomach. Her symptoms consisted of tremor, formication, pains in the chest, and muscular weakness —all of which soon vanished entirely on the removal of their cause.

The post-mortem appearances present nothing peculiar, except a very perceptible smell of ether, which is scarcely ever absent, and is known to persist for some time after death. There are no other characteristic symptoms.

The treatment must be similar to that of poisoning by chloroform.

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[1] Virchow und Hirsch, Jahresbericht (*Husemann*). 1870.

CHAPTER IV.

POISONING BY CHLORAL HYDRATE.

The more this anæsthetic, introduced into surgical practice by Liebreich[1] in 1869, has grown into favor with medical practitioners, the more indubitably, though slowly, has its nature as a poison come into notice; partly from observations on patients, and partly by pharmacological experiments. Although this new remedy is a very valuable one, we have learned by the experience of the last few years that its use is not always devoid of danger even in the most skilful hands. The more firmly it is established as a remedial means of undoubted usefulness, the more incumbent is it on toxicologists to discover its injurious effects, and to study the circumstances which cause these to replace the beneficial results which are wished for when it is prescribed. The hydrate of chloral ($\Theta_2Cl_3\Theta H, + H_2O$) is met with in the form of white crystals, which possess more or less of a characteristic penetrating smell, according to the purity of the substance. It is easily soluble in water, and the solution is neutral to test-paper, and gives rise to a peculiar aromatic and rather unpleasant taste, which is associated with a feeling of scratching or soreness in the throat. It is now manufactured in very large quantities for medicinal use.

Chloral is absorbed and received into the general circulation in the same way as all other bodies which are soluble in water and diffusible. It is subject to the ordinary laws of diffusion, and its absorption is therefore possible wherever an exchange can take place between its solution and the fluids of the body; it can therefore be absorbed by mucous and serous membranes, and in the subcutaneous areolar tissue. The absorption through serous membranes is the slowest of all. Porta[2] has never seen the general effects of chloral after the injection of a considerable quantity into the sac of a hydrocele, though he has done this

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[1] Das Chloralhydrat, etc. Berlin. 1869.

[2] *Husemann*, Ueber Chloralhydrat. Schmidt's Jahrb. Bd. 151. 1871.

experiment repeatedly. As it is volatile, though only slightly so, a small portion may pass into the blood in the form of vapor, through the membrane of the air-cells of the lungs. The question, in what way and in what form chloral is eliminated from the bodies of animals is not yet settled, in spite of numerous experiments. Liebreich found neither chloroform nor chloral in the urine of animals poisoned with chloral. On the other hand, he found an increase of the chlorides. Byasson says that he has found salts of formic acid. Hammarsten[1] also found no chloral in the urine, and none at all in the expired air, but he found it in the blood of animals thus poisoned. Hermann[2] has lately succeeded in showing, by means of the isocyanphenyl reaction of Hofmann, that small quantities of chloral are present in the urine of men who are chloralized. No trace of chloroform was discovered by him in the fluid.

Liebreich's theory that chloral is decomposed in the blood into chloroform and formic acid has given rise to a long series of researches, the general result of which is best expressed by saying that the question must still be regarded as an open one. The similarity in the effects of chloroform and of chloral, and the fact that this splitting up of chloral does occur in alkaline fluids, justify the opinion that some similar process occurs in the blood when chloral is taken. Hammarsten, Porta, Gubler, and others have, however, rendered it pretty certain that we must not reckon the blood as identical with alkaline solutions merely because its reaction is alkaline. Hammarsten could find no chloroform in either the blood or the expired air of chloralized animals. Radjewsky[3] and Frln. Tomascewicz[4] met with similar negative results in relation to the elimination of chloroform by the lungs in such cases. The latter made use of the very delicate reagent of Hofmann in the tests which she carried out in Hermann's Institute. Richardson, Roussin, Personne, and Byasson[5] met with positive results, in consequence of which they

[1] Compare *Husemann*, loc. cit.

[2] Experiment. Toxikolog. p. 272.

[3] Centralblatt f. d. med. Wissenschaften. 1870.

[4] *Hermann*, Experiment. Toxikol.

[5] Compare *L. Lissonde*, De chloral hydraté, etc. Paris, 1874. Lissonde, certainly

became defenders of Liebreich's theory. Hermann brings very grave objections against their experiments. There is another body of the *fatty acids* series, the trichloracetic acid, which is similarly split up by alkalies into chloroform, etc., and actually reckoned by Liebreich as a narcotic. It was, however, found to be absolutely devoid of narcotic properties by Hermann. In the same way he disposes of the narcotic action of iodal. According to Liebreich's theory iodoform ought to be formed from this substance in the blood. It has, however, no narcotic action. Until further facts are known we must, therefore, leave any possible formation of chloroform out of sight in our explanation of the operation of chloral. Its effects are indeed similar to those of chloroform, but not more so than those of other organic chemical anæsthetics. We must, therefore, for the present, accept chloral as a new member of a series of anæsthetics whose effects all have a family likeness, but can, in the present state of our knowledge, be only very imperfectly explained in either their physiological or their chemical relations.

The stroma of the red blood-corpuscles is not dissolved by chloral, but swells up under its influence (Hermann). Ritter and Feltz,[1] who injected different quantities of chloral into the veins of dogs, found, after repeated injections and long continued narcosis, that the blood-corpuscles were misshapen and deprived of their elasticity. The plasma of the blood was colored red (hæmoglobin in solution) and hæmoglobin crystals very readily formed on object-glasses, and even the urine contained blood-coloring. Besides this, the blood had absorbed little more than half its normal proportion of oxygen. In a very concentrated state, chloral has a corrosive or escharotic action; on fresh wounds, on muscles which are laid bare, on mucous membranes, and suppurating surfaces it produces a superficial white scab, and it causes redness and vesication of the skin when applied externally.

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without any idea of *Hammarsten's* experiments, mixed blood and bicarbonated salts and chloral together, and in both experiments obtained chloroform reactions. *Hammarsten*, however, shows that this is no proof that the same thing happens in the blood which circulates.

[1] Bullet. général de thérapeut. 1873.

From the remaining physiological investigations we learn that chloral, like all analogous remedies, very materially affects the functions of the higher nerve-centres, and in some circumstances causes death by paralyzing the heart, or by stopping respiration. In animals of different classes it causes a diminished frequency of the heart's action, apparently by exciting the cerebral origin of the vagus nerves; in larger doses, it paralyzes the action of the heart (Radjewsky).[1]

In a similar way, small doses diminish the frequency of the respirations, whilst larger ones sometimes cause stertorous breathing and stoppage of breathing altogether. If we were to enter into details on these matters, we should have to repeat almost the very expressions we used when speaking, in relation to these effects, on the action of chloroform and ether. But we think Heidenhain's[2] experiments, establishing the paralyzing effects of chloral on the centre for vascular nerves, are of great significance, because a great many of the injurious results of the therapeutic use of chloral can be explained by these. In experiments on animals, this paralysis is manifested by an enormous diminution of the arterial blood-pressure; in men, on the other hand, the feeling of weakness, and the ultimate failure of the radial pulses, point to considerable disturbances in the vaso-motor sphere. The practically interesting effects sometimes produced by chloral on human beings, and more particularly in those mentally afflicted, will be discussed in their appropriate place. As yet, physiology has given no explanation of them.

As chloral hydrate is still far too commonly prescribed in excessive doses, it is easy to explain why the majority of cases of poisoning by this substance occur in medical practice. Of late, however, both in England and Germany, there have been several cases in which it has been voluntarily taken by persons not in the medical profession. As a rule, these are persons who suffer from want of sleep (insomnia) and are delighted with this drug, but too commonly take it in excessive doses. If we consider how short a time has elapsed since the discovery of chloral,

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[1] Centralblatt für die Med. Wissensch. 1870.

[2] Pflüger's Archiv. Bd. IV., p. 551, et seq.

the great number of these unfortunate cases must not only strike us with surprise, but ought to furnish a strong motive for the exercise of caution in prescribing its use.

All authors agree as to the great difference between the susceptibility of different patients as regards the effects of chloral. There have even been known persons who appeared to be absolutely unaffected by this drug, and who have been able to take enormous quantities, not only without the usual effect, but without any injury accruing; and there are other cases where very small quantities have produced very unpleasant effects. The temperament or constitution of patients seems, according to our experience, not to have any effect in regard to susceptibility to the effects of chloral, although Porta (loc. cit.) holds that children and delicate patients are more amenable to its effects than others, which seems probable on *a priori* grounds.

The only pathological conditions specially noted by writers on this subject as modifying the susceptibility to the influences of chloral are alcoholism and frequent indulgence in the use of stimulants. These greatly hinder the effects of chloral. Although chloral has been very largely used in psychical diseases, yet no very definite conclusions can as yet be drawn from this experience. However, paralytic patients appear to be specially obnoxious to the injurious effects of chloral on the vaso-motor nerves. Whether the injurious effects of chloral are most prone to occur in cases of failing heart and vascular degenerations (such as atheromatous and similar processes), is also not definitely settled, though it seems likely that such conditions may predispose to danger. It is also as yet undecided how far chloral exhibits what may be called a *cumulative* action, or whether it belongs to those substances to which the system gradually becomes accustomed. Although it is pretty well established that, if we desire to keep up the hypnotic action in long-continued use of chloral, we must go on increasing the doses, it is at least doubtful whether the power of the nervous system to resist its injurious effects increases in at all the same proportion. The phenomena of the so-called chronic poisoning by chloral (which we shall comment on by and by) do not by any means negative the idea of its accumulation in the system. The poisonous and fatal doses

of chloral hydrate can only be approximatively determined. We have gradually acquired by experience a knowledge of the fact that doses of seventy-seven grains, which used to be considered quite a safe dose for grown-up people, should by no means be prescribed as a mere matter of routine, nor indeed without very careful consideration. Indeed, fatal cases have occurred, not only from this dose, but from even smaller ones, and that quite suddenly. So far, therefore, as a general rule can be established, we must consider forty-six grains as the maximum limits for safety. For children and delicate adults, still smaller doses must clearly be prescribed.

The symptoms produced by chloral, so long as they are simply medicinal and salutary, are those of simple narcosis. This occurs, as a rule, without any particular stage of excitement, and without any peculiar subjective symptoms, in the form of a quiet sleep, the duration of which varies very greatly, according to the surroundings and the individual peculiarities of those who are *chloralized*. As a rule, there are no particular sequelæ, and no recollection of the beginning of the sleep, or of dreams during the slumber. Occasionally it leaves behind it, for a short time, some headache, want of appetite, and muscular weakness. The objective phenomena of this moderate or normal chloral narcosis, are also not very characteristic. The temperature of the skin, and the frequency of the pulse and of the respirations, have been found diminished. The pupils are affected but slightly; sensation is not so keen as before, but is not so far abolished as to permit the performance of very painful operations. The excretions are not affected in any manner deserving of special notice. These symptoms, which are all more or less modified in special cases, are sometimes specially so by the occasional occurrence of symptoms of excitement, like those which are the rule in chloroform narcosis. In such cases, the persons under the effects of chloral give one the impression of being drunk, because their excitement is manifested by talking, laughing, crying, and all sorts of movements. This stage of excitement may either gradually terminate in the return of consciousness or may pass into the customary narcotism. Even in cases where the symptoms of chloral narcosis are more noticeable, there is, as a rule, no strik-

ing outward warning of the approach of danger or death. It is far more common for these to set in suddenly, so that, for example, soon after the patient has taken the dose, or a little later, he sinks into a helpless condition, from which he never wakes again. More rarely death has been observed to be preceded by dyspnœa and stertorous breathing (thus approximating to the type of asphyxia). The symptoms of chronic poisoning by chloral, which have hitherto been noticed chiefly in asylums, may be divided into three distinct classes.

In the first class we have the often observed disorders of digestion, induced by the long-continued use of chloral, and these are indisputably due to its local action as an irritant. When affections of this kind occur in persons who are already in a depressed bodily condition, especially in paralytics, it is easy to understand that they may prove somewhat serious, and even hasten the fatal termination. Pelmann has published cases of this kind. In one case jaundice supervened, and the patient died in seven days, having been somnolent nearly all the time.

In the second group we may class the numerous cases of skin diseases observed after long use of chloral. They may assume the forms of various exanthems (erythema, urticaria, papulæ, purpura, petechiæ, etc.), and they clearly prove themselves to be exanthems due to poison (Intoxicationsexantheme), since they generally vanish again very quickly when the drug is discontinued.[1] With these we may class the cases in which the use of chloral has given rise to more or less extensive bedsores (see Reimer[2]). These have occurred, for the most part, in cases where the patient, after large doses of chloral, has lain a long time in one position. Reimer has observed the development of more or less deep ulcers and wounds from mere circumscribed redness and swelling of the skin, with the formation of blisters on the trochanters, knees, knuckles, tips of fingers, and even on the face and ears and other parts. Lastly, Schuele[3] and Jolly[4]

[1] Consult on this *Husemann* (loc. cit.) and the Jahresbericht über die Fortschritte, etc., of *Virchow* und *Hirsch*. 1871 and 1872 (art. Chloral).

[2] Allg. Zeitschrift für Psychiatrie. Bd. 28. 2. 1871.

[3] Allg. Zeitschrift für Psychiatrie. Bd. 28. 1. 1871.

[4] Bayer. ärztl. Intell.-Blatt. 1872. No. 14.

have quite recently observed a number of symptoms in lunatics treated with chloral, which must indisputably be referred to anomalies in the innervation of blood-vessels.

Along with symptoms of increased action of the heart, generally in consequence of very moderate use of spirits, there suddenly occurred an erythematous blush, spreading itself over a large surface of skin, sometimes on the face, and then with hyperæmia of the conjunctivæ and of the posterior surface of the eyes (retinæ), and sometimes in other parts of the body. Schuele noticed at the same time a change of behavior in his patients. All these symptoms perfectly vanished when the chloral was left off. If we exclude the gastric disorders, which are easily explicable, almost all the other symptoms of chronic chloral poisoning may be referred to the anomalies of the circulation, which are brought about by the paralyzing influence of the chloral on the vaso-motor centre — on which we have before insisted so strongly. Even the tendency to bedsores may be thus explained. Hitherto no characteristic post-mortem appearances have been described in fatal cases of chloral poisoning. The treatment of cases of acute poisoning must clearly be analogous to that for poisoning by chloroform. For the chronic forms, as a rule, it is sufficient, along with appropriate regimen, to insist on a timely discontinuance of the drug which is the source of the mischief.[1]

CHAPTER V.

POISONING BY SOME OTHER ANÆSTHETICS.

Besides chloral, chloroform, and ether, several other members of the so-called "Fatty Acids Series" have of late years sought introduction into medical and surgical practice. Although the majority of these have been introduced as substitutes for chloroform, on the ground that they were free from the dangers which attend the use of this agent, yet most of them, as soon as they

[1] See a paper by the translator in Vol. IV. of the St. Andrew's Medical Graduates' Transactions, p. 222.

have been put to the test, have proved at least quite as dangerous, if not more so, than chloroform, which they were introduced to supersede.

Repeated cases of death, attributable to their use, have up to the present time prevented any of them from obtaining anything like general acceptance from the profession. Most of these substances agree in all essential points as regards their operation on the system and their properties, with what has been already ascribed to chloroform and ether. It will therefore suffice, for the present purposes of this work, if we collect together the most important toxicological observations which have been published as regards the most important of these anæsthetics.

I. *Amylene.* C_5H_{10}.

This hydrocarbon, in which the carbon is not fully saturated, is distinguished by its peculiar smell, somewhat resembling the odor of garlic. Its boiling point is 35° Centigrade = 95° Fahrenheit ; its specific gravity, 0.65. It was long ago repeatedly tried as an anæsthetic in surgical operations, at the recommendation of Dr. Snow. Very numerous experiments on both men and animals have confirmed the powerful anæsthetic effects of this substance, without our being able to discover that its effects differ in any very essential manner from those of similar substances. Nor can we find that it possesses any peculiar advantages, although it has been lauded in extravagant terms. That it is not any safer than chloroform was shown by the occurrence of two fatal cases very shortly after Snow had recommended its use. These cases were witnessed by Snow himself. The death was by narcosis, and the symptoms were similar to those of death by chloroform.

II. *Bichloride of methylene.* CH_3Cl_2.

This substance, which is not only very like, but closely allied, to chloroform in its composition, has been particularly recommended by Richardson and Junker. Except in England, where it was a good deal used in several hospitals, it does not appear to have found much favor with the medical public. Richardson has lately recommended a mixture of bichloride of methylene and sulphuric ether, under the name of methylether, as a very useful anæsthetic. Three cases of death from the former and

one case of death from the latter secure for these substances a place amongst poisons. There is, however, no essential difference between their effects and the mode of death to which they lead and those of chloroform. We must, therefore, as before, refer to that chapter for details.

III. *Bichloride of ethylidene.* $C_2H_4Cl_2$. (Boiling point 60° to 62° C. = 140° to 143.6° F.)

This substance was recommended by Snow and Liebreich as an anæsthetic, and from the favorable accounts of several authors it would appear that the results of its use have generally been fortunate. Yet already one death has occurred from its use in one of the Berlin clinics. We must refer to special works for information as regards the differences between these substances and chloroform in their effects. As regards their poisonous properties we consider ourselves justified in saying that no important difference is yet known.[1]

No cases of poisoning have been hitherto reported from the use of *nitrite of amyl* or of *croton chloral.* Interesting as these medicines are, we are therefore compelled to pass them over without further notice.

IV. *Nitrous oxide* (laughing gas).

Although the narcotic effects of this gas were discovered by Sir Humphrey Davy at the beginning of this century, and although they were observed by numerous authors who succeeded him, it was first introduced into dental practice as an anæsthetic some thirty years ago in North America. Of late years its use for this purpose by dentists has attained to very large proportions in Europe, and general experience is unanimous in the verdict, that for operations which only last a very short time, such as the extraction of teeth, it is a very serviceable, and if properly employed, a very safe means of benumbing pain.

The mode of action of this gas was first placed in its proper light, and confirmed by experiments, by L. Hermann, viz., that when breathed without admixture of atmospheric air or oxygen, like hydrogen, and other indifferent gaseous bodies, it kills by suffocation (or simple deficiency of oxygen). Inhaled in a mix-

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[1] Compare, as regards this, the references of *Husemann* in the Jahresbericht über die Fortschritte der Medicin of Virchow and Hirsch. 1865–74.

ture in the proportion of four of nitrous oxide to one of oxygen it produces in human beings a cheerful narcosis, like inebriation by alcohol, which quickly disappears when the inhalation of the gas is discontinued. Consciousness and sensation are never perfectly abolished during this condition. There can, therefore, be no doubt that nitrous oxide, like other anæsthetics (chloroform, ether, etc.), affects the functions of the cerebrum. In animals this mixture of gases seems to have no effect.

The mode of using this gas by dentists differs from that in which other anæsthetics are used, because the access of the oxygen of the atmosphere is prevented, and only the pure unmixed nitrous oxide is used as the anæsthetic. In consequence of this the narcotic effects of the gas are combined with the first stage of suffocation, so that deep narcosis speedily occurs, during which operations which only last a few seconds can be performed quite painlessly. It follows, as a matter of course, from what has been said, that if the experiment be prolonged to a period of a few minutes, death by suffocation must necessarily result. As loss of consciousness and anæsthesia also occur in the first stages of suffocation, without breathing in any narcotic gas, it is somewhat doubtful how far the gas participates in the effect, when used in dental practice in the manner described. A narcosis which greatly resembles this can be produced by the inhalation of hydrogen whilst the atmospheric air is simultaneously excluded.

The enormous number of teeth extracted at the present time by the aid of this gas, without any accident, would seem to show that there is no very great danger in it. But some few fatal cases which have occurred, either during or after the narcosis, show that it is not absolutely devoid of danger. These, however, appear to be simply and solely due to suffocation, and the gas itself appears innocent. This is not the place to lay down rules for the safe use of this gas; moreover, it appears very doubtful whether the unfortunate cases ought to be reckoned as cases of poisoning at all. The indications for treatment in such cases are precisely those which are laid down in surgical manuals for the treatment of asphyxia from other causes.

CHAPTER VI.

POISONING BY CARBONIC OXIDE, AND BY THOSE GASEOUS MIXTURES IN WHICH CARBONIC OXIDE IS THE ESSENTIAL INGREDIENT (AS POISONING BY THE VAPOR OF CHARCOAL AND POISONING BY COAL-GAS USED FOR LIGHTING)

Carbonic oxide plays a prominent part amongst poisonous gases. It is a colorless, and almost odorless gas, which is very slightly soluble in water, and burns in the air with a pale bluish flame. It is easily generated when coals or charcoal are burnt with insufficient access of air, and besides this, it is an ingredient in gas used for illumination.[1] In most cases this poison is received into the system by the organs of respiration; from the surface of the lungs it diffuses itself into the capillaries. Whether carbonic oxide may gain access to the blood in other more indirect ways, seems doubtful, and there are no trustworthy experiments on this point.

Friedberg[2] has contradicted Husemann's[3] assertion that Carminati had proved the possibility of the absorption of the vapor of charcoal through the surface of the body. Carminati's experiments did not relate to carbonic oxide at all, but to the vapor of sulphur (Schwefeldampf).

Nor is anything known accurately as to the ways in which carbonic oxide is eliminated from the system. On this account the manner in which this poison acts upon the system, and especially on the blood, deserves especial study. This gas is not easily soluble in blood, though more so in this fluid than in water, which will only dissolve about $\frac{1}{16}$ of its volume. In regard to its solubility in blood it is far inferior to carbon dioxide, and to hydrogen sulphide. Claude Bernard[4] found that blood could absorb 9.4 volumes per cent. of carbonic oxide, and confirms Nysten's[5] assertion, that large quantities of this gas,

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[1] See also the chapter on Etiology.

[2] Die Vergiftung durch Kohlendunst. Berlin. 1866. S. 79.

[3] Handbuch der Toxikologie. S. 656.

[4] Leçons sur les effets des substances toxiques. p. 157.

[5] Recherches de physiologie et de chimie pathologiques. Paris. 1811.

injected suddenly into the veins of an animal, brought about death mechanically by gaseous embolism, which does not happen after injection of carbon dioxide or sulphide of hydrogen in gaseous form.

Small as the quantity of this gas absorbed by the blood may be, it suffices to bring about very extensive and serious changes in its properties. The researches of Claude Bernard (loc. cit.), of Lothar Meyer,[1] and Hoppe-Seyler[2] have established the fact that carbonic oxide displaces oxygen from the blood, and enters into combination with the coloring matter of the blood in such a way as to render this incapable of absorbing more oxygen. The outward sign of this change is manifested by a peculiar, bright cherry-red coloration of the arterial as well as venous blood; whilst in the spectrum of blood containing carbonic oxide the two usual bands of oxyhæmoglobin are replaced by two others, which appear nearer to the violet end of the spectrum, and these carbonic oxide bands exhibit the special character of *not* vanishing on the addition of reducing agents, as those of oxyhæmoglobin do. The compound of hæmoglobin with carbonic oxide is crystallizable just like oxyhæmoglobin. It is more solid than this, and is less easily evaporated in vacuo. However, it can be decomposed by passing other gases through the blood and also by the use of the air-pump, just like oxyhæmoglobin; so that we cannot help considering the two compounds as very analogous one to the other.[3] One especial result of these investigations is to show that carbonic oxide combines with hæmoglobin just in the same volumetric proportions as oxygen does. It seems almost unnecessary to try to prove that this relation of carbonic oxide to the blood, which equally occurs in the living body, must to a very great extent explain its poisonous properties. It makes the further reception of oxygen, and therefore life itself, impossible, and so much the more as, owing to the stability of the compound, the whole mass of the blood very speedily becomes robbed of its vital properties, provided only

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[1] De Sanguine oxydo-carbonico infecto. Inaug.-Dissert. Breslau. 1858.

[2] Virchow's Archiv. Bd. 11. 1857.

[3] Consult. on this, *Zuntz*, Pflueger's Archiv, V.; *Donders*, ibid.; and *Podolinski*, ibid. VI.

that the poison is present in sufficient quantities in the medium respired. Notwithstanding this, there is by no means such unanimity on this point amongst those who have written on the subject as we might expect, *a priori*. Whilst one set considers that the symptoms of poisoning by carbonic oxide are perfectly explained by the above theory, and regards the whole symptoms as essentially a form of suffocation produced by want of oxygen (Claude Bernard [loc. cit.], Hoppe-Seyler [loc. cit.], Pokrowsky,[1] Friedberg[2]), others insist most strongly on disturbances in the circulation (atony of the muscular coat of the blood-vessels), which must be considered as a result of poisoning by carbonic oxide, not dependent on its power of robbing the blood of oxygen (Klebs[3]). They consider that this poison acts like a narcotic on the organs of the central nervous system (Siebenhaar and Lehmann[4]).

Pokrowsky has endeavored to establish the identity of poisoning by carbonic oxide with other forms of suffocation (breathing of nitrogen, hydrogen, carbonic acid, and mechanical occlusion of the air-passages) by a careful physiological analysis of the symptoms. The results of this agree essentially with those of an independent inquiry of the same kind made by Traube,[5] and founded on experiments. Indeed, the results of this inquiry are a most evident agreement in the physiological effects of the various modes of suffocation. Although we may not always agree in every minute point with Pokrowsky's arguments, yet his conclusions are undoubtedly justified by Traube's experiments. Pokrowsky's experiments show the following results: That after the first breathing of a medium poisoned with carbonic oxide, the blood-pressure, which was first considerably increased, soon sinks considerably with a simultaneous considerable retardation or slowing of the pulse. This second phase in the phenomena of the circulation in poisoning by carbonic oxide has all the characters of a blood-pressure and pulse-curve due to peripheral irritation of the vagus. This stage is succeeded by a third, in which a still lower grade of blood-pressure, and a shallow, but more frequent, pulse are met with. Unless artificial respiration is resorted to in this stage, death follows with constant increase of the symptoms last named up to the moment of death. Division of the vagus nerves in the second stage completely annuls it, but under certain conditions only retards it, when the operation has been done before the poisoning; as for instance,

[1] Archiv f. Anat. und Physiol. 1866.

[2] Die Vergiftung durch Kohlendunst. Berlin. 1866.

[3] Virchow's Archiv. Bd. XXXII.

[4] Die Kohlendunstvergiftung. Dresden. 1858.

[5] Gesammelte Beiträge zur Pathologie und Physiologie. 1. Band.

when the attempt at poisoning has been repeated several times in rapid succession, or when the animal is already suffering severe dyspnœa as the result of the previous section of the vagus. In the third stage (of low blood-pressure, with small and frequent pulse) irritation of the medulla oblongata, or of the cervical cord, is followed, as a rule, by a considerable increase in the blood-pressure.

In the present state of physiological opinion on the circulation, these views of Pokrowsky, which are established by a long series of experiments, all pointing in one direction, are explained in the simplest manner by considering them as simple results of the deficiency of oxygen. This at first causes a transient increase in the blood-pressure, by irritation of the vaso-motor centres, which is succeeded by a period of central (and perhaps peripheral also) irritation of the vagus, in its turn succeeded by paralysis of the vaso-motor centres.

All these events are also seen to occur if we stop the aeration of the blood in any other way, provided it be not done too suddenly. Pokrowsky differs from this conclusion, inasmuch as he believes the first as well as the last-named stages to be dependent on excitement or excitability of an excito-motor centre for the heart, situate in the medulla oblongata. He does not hold our view of the case to be valid, because he sees no increase of pressure follow compression of the aorta in the third stage. On this account he admits a weakening of the action of the heart, which may be temporarily removed by irritation of this centre in the medulla. We have felt obliged to differ from him, because the existence of this excito-motor centre in the medulla, which, it is well known, von Bezold admitted in his day, is at the present moment more than doubtful.

Pokrowsky also seems to us to be decidedly wrong in believing that contraction of the (small) arteries coincides with the sinking of the (blood-)pressure; and still more so when he brings this forward as an argument against Klebs's theory of poisoning by carbonic oxide, for this is well known to be based on atony of the arteries. The effects previously quoted from his paper on irritation of the cervical cord, show clearly that P. has probably deceived himself in this matter, and observations on the calibre of the vessels of the mesentery or other parts, with or without a microscope, are at present not very reliable modes of physiological investigation. Klebs, indeed, despairs of any generally acceptable view of the true nature of carbonic-oxide poisoning, but he pronounces in no doubtful terms against the view of the symptoms given above; and he considers the atony of the vessels as a sort of middle term between the poisoning and the asphyxia which finally succeeds it. But all controversy apart, there is atony of the vessels, though it may not be very great, in all stages of the whole affair. Klebs considers the want of suffocative spasms as a sufficient reason for not assigning the symptoms in this kind of poisoning to mere deficiency of oxygen. And he draws particular attention to the general occurrence of sopor in poisoning by carbonic oxide—a symptom not noted in simple abstraction of oxygen. Lastly, whilst he will not assert the absolute impossibility of the two conditions being alike, he thinks that at least their identity is not proved. Whilst agreeing with him in this last opinion, we cannot accept all the arguments and experiments on which he founds it. As regards the absence of

convulsions or spasms, Klebs contradicts almost all who have written on the subject. Though this symptom may be wanting or imperfectly developed in some instances, it is present in an overwhelming majority of the cases, and even some of Klebs's cases seem not quite free from doubt on this point. Nor can we agree with Klebs in the importance he attributes to sopor. Against this doubtful symptom, we have to set the general agreement in the disorders of the circulation produced both in carbonic-oxide poisoning, and also in the various forms of suffocation. We must agree with Klebs as to the significance of the vascular paresis, but not in attributing the comatose condition met with in poisoning by carbonic oxide to direct blood-pressure on the cortical surface of the brain produced by the vascular dilatation. Simple reflection will show us that, in every paresis of the vaso-motor centres, there must result a relative anæmia of the central organs of the nervous system; because whilst the efflux through the veins is unhindered, the afflux through the arteries is diminished; and since the chief mass of the blood is circulating through the great vascular domain of the abdominal vessels, it is clear that the mean blood-pressure is diminished. Vascular paresis is therefore more likely to cause anæmia than hyperæmia of the cerebral vessels. It is only one link in the chain of the symptoms of poisoning by carbonic oxide, and necessarily results from the gradually decreasing vital excitability of the organs of the central nervous system through the failure of oxygen.

The modern classification of carbonic oxide as a narcotic poison, warmly advocated by Siebenhaar and Lehmann, need not detain us, because no fresh facts or explanations are given. The expression, "narcosis," is a vague term for a number of things which differ widely as regards their physiological basis. There are, however, a few facts not mentioned, which seem to contradict any special action of carbonic oxide on the nervous system. Frogs do not die much more quickly in this gas than they do in other indifferent gaseous mixtures deprived of oxygen; and invertebrate animals, which do not possess blood containing oxyhæmoglobin, are not all affected by it.[1] The nerves and muscles of the frog, and the heart of the same animal, are not at all affected by this gas as regards their vital properties. The explanation of the various symptoms in poisoning by carbonic oxide will be dealt with, as far as practicable, in the section relating to the Symptomatology.

It is not possible, in the present state of our knowledge, to definitely decide for or against either of these theories of poisoning by carbonic oxide. However numerous the facts which tend to make us accept the theory of a pure toxæmic action of this gas, we must not forget that there are others which cannot be reconciled with this view. It has very properly been insisted on that, even in the corpses of men killed by carbonic oxide, oxygenated hæmoglobin can be detected in the blood by the spectro-

[1] See *Pokrowsky*, loc. cit.

scope; and we are therefore still uncertain how much oxygen must be withdrawn from the system before toxic symptoms are induced, or whether, in a given case, the actual deprivation or removal of oxygen has been sufficient to explain the symptoms in their entirety. The remarkable immunity of some persons as regards this form of poisoning would seem to support the view that the abstraction of oxygen is not an essential factor in the action of carbonic oxide on the nervous system. But it must be remembered that some people can bear to be deprived of oxygen much better than others, whilst we have no very satisfactory examples of an analogous immunity as regards any specific nerve-poison.

Experiments made by injection of blood saturated with carbonic oxide into the circulation of animals, such as those of Claude Bernard, Klebs, and Traube, have not hitherto furnished any certain results. As oxygen is not withdrawn in these experiments, and yet symptoms of poisoning occur, we might conclude that this was in favor of a direct toxic action of carbonic oxide. But the quantity which can thus be introduced is, after all, but little, and the symptoms produced have not amounted to much more than slight dyspnœa. The antagonism which, as Klebs asserts, exists between carbonic oxide and ergotin, might be held a weighty argument against the toxæmic and in favor of the specific poisonous action of carbonic oxide. For ergotin cannot supply the deficient oxygen, and if, notwithstanding, it is really antagonistic, Klebs's theory would seem to gain support. But, alas! this action of ergotin seems not sufficiently proved. Klebs's report on these ergotin experiments gives no figures for the mean blood-pressure before and after the poisoning by carbonic oxide, and after the ergotin injection, so that the particular action of the ergotin on the diminished blood-pressure cannot be estimated. And again, we are left in doubt by this report whether the administration of the gas was continued or broken off after the injection of the ergotin. A true antagonism could only be admitted if the poisonous symptoms decreased in spite of continued inhalation of the carbonic oxide. In all the cases in which the carbonic oxide was removed, we are led to doubt whether the access of oxygen, and not the ergotin, proved the

antidote, or at least did the good which is recorded. Lastly, the sequelæ of carbonic oxide poisoning, so often met with, require comparison with the facts which are so difficult to reconcile with the simple abstraction of oxygen. Further experiments may be needed to remove the difficulties which exist in the way of either theory. In the meanwhile, therefore, our judgment must be suspended.

Chemically pure carbonic oxide is very seldom the means of poisoning. In general, this poison is mixed with other, in part indifferent, in part equally injurious gases, so that, however strongly inclined, we can scarcely regard the cases as simple cases of poisoning by carbonic oxide. Yet multiplied experiences have taught us that the danger of these mixtures depends undoubtedly on the carbonic oxide present, and that, apart from this, the gaseous mixtures produce but very trifling symptoms. We may, therefore, practically disregard the admixtures.

The most important compound of this kind is the *vapor of charcoal*, which contains, in addition to carbonic oxide, large quantities of carbonic acid, and some traces of the carbides of hydrogen. Any certain estimate of the relative quantities of these gases in the *vapor of charcoal* is not possible. According to Eulenberg, most of the analyses have given about 2.5 per cent. of carbonic oxide and 24.6 per cent. of carbonic acid. It is easy to understand that in general there is also an admixture of atmospheric air. Sometimes hydrogen sulphide and combustible gases are also mixed with it.

The second mixed gas of which carbonic oxide forms the most important constituent is the *coal-gas used for illuminating purposes*. We must, therefore, consider cases of poisoning by the vapor of charcoal and those due to lighting-gas.

The special etiology of poisoning by the vapors of charcoal almost always depends on the imperfect combustion of materials rich in carbon (wood, charcoal, anthracite, coke, etc.), and the commonest cases of all are those due to defective heating apparatus (stoves, braziers, etc.). When the stove-pipes, destined to carry away the products of combustion, become choked with soot, or when the valves are closed, the gases generated by combustion can only accumulate in the space which is being warmed,

and those persons who remain in the place where the stove is are poisoned; the more easily the smaller the room, or the more defective the ventilation. An opinion formerly prevailed that the poisonous gas is most abundant in the lower portions of the room, just above the floor, but it is now known that the poisonous mixture of gases is most dense, as might be expected, close to the burning materials. But they may be capable of doing a great deal of harm at a very considerable distance from the place where they are generated.

Cases are on record in which the vapor of charcoal has diffused itself through several large rooms, or through communicating flues, into stories quite separate from the floor on which it was generated. Even in the open air, in the immediate vicinity of charcoal ovens, there may be very dense accumulations of the vapor. There are several cases in which the smouldering of beams under the floor or in walls, from accidental combustion, has caused danger in dwelling-rooms from the vapor produced. The unskilful use of braziers and warming-pans, and the like circumstances, naturally belong to the same category and need not detain us. Fires in mines and other underground places (tunnels, etc.), and blasting operations, are especially dangerous on account of the defective circulation of air, and these generally afford numerous victims.

What has been called the "Sapper's and Miner's disease" (Minenkrankheit) has been attributed to carbonic oxide poisoning. According to recent investigations by Polleck,[1] who took advantage of a siege in the fortress of Neisse to examine the constitution of the gases generated in mines by the explosion of gunpowder, the percentage of carbonic oxide is not any considerable quantity except at the beginning of the blasting operations, and is gradually diminished in consequence of a variety of causes, which need not be detailed here. In unison with this the sappers and miners suffered most severely at the beginning of these operations, and their sufferings gradually decreased, both in severity and in number. In the meanwhile, it is by no means certain that these conditions are identical with poisoning by carbonic oxide.

The majority of cases of poisoning by carbonic oxide are due

[1] Die chemische Natur der Minengase und ihre Beziehung zur Minenkrankheit. Berlin. 1867. The Chemical Composition of the Gases in Mines, and their Relation to the Miner's Disease.

most certainly to want of due caution, or to accident; yet there are many recorded cases in which the poison has been used for suicidal purposes, and a few in which it has served the purposes of murderers. In Germany suicides by carbonic oxide are very seldom observed, while in France this mode of suicide is excessively common.[1]

Poisoning by coal-gas used for lighting is far more rare.

The quantity of carbonic oxide required to kill is not easy to estimate; and the most accurate estimates which are recorded refer exclusively to the lower animals; we therefore think it unnecessary to reproduce them.[2] The question as to individual predisposition, or sensitiveness to carbonic oxide, has been previously mentioned. It has been observed, in some cases, that different persons, exposed to the same mixture or quantity of the gas, have been variously affected; some even appearing to exhibit a perfect immunity. As regards this fact, which requires more precise confirmation, we can give no explanation. Klebs attributes it to different conditions of the heart in different people, but this is not easy to demonstrate. It is quite certain that children succumb rapidly to the action of this poison, which may perhaps be due to the great activity of the respiratory process in young people.

There is a pretty general agreement amongst authors as to the symptoms produced by carbonic oxide in human beings.

The first subjective symptom which occurs after breathing the poison is a burning feeling in the skin of the face (Klebs[3]), quickly followed by giddiness and headache, which gradually becomes more intense; the chief site of this headache is in the temples. Experimentalists and those poisoned agree in this. This headache or pain is generally associated with a subjective feeling of strong pulsation in the temporal arteries. Occasionally, even in this prodromal stage, we get feelings of nausea, and of oppression in the stomach and in the precordial region. Very often, though not invariably, these are associated with a variety of subjective sensations, as motes dancing about (muscæ voli-

[1] As regards the statistics of this consult *Husemann's* Toxikologie. pp. 60, 654.

[2] See *Husemann's* Supplement. loc. cit. p. 101.

[3] Loc. cit. p. 469.

tantes), noises in the ears, and the like, symptoms which indicate, to a certain extent, the severance of the sensorium from the domain of reality, and the transition to perfect loss of consciousness.

The psychical condition which precedes the latter is sometimes a distress of mind, full of agonizing tortures, sometimes a sort of pleasant and ecstatic feeling ; but the former appears to be the rule. The access of insensibility is either a sudden withdrawal from consciousness, like a stroke ; or it is preceded by pronounced phenomena of great discomfort—anxiety, nausea, and excitement—which often lead the poisoned persons to make an effort to leave the poisonous atmosphere in which they find themselves, or to try to get air by opening the windows, etc. Very often the insensibility attacks them during this very effort, so that the poisoned person falls down half way to the window or door, and lies there unconscious. At this stage all perception and consciousness of anything further are lost, so that we cannot look to the victims for any further account of themselves. The subjective symptoms which are noted in cases of recovery or restoration to consciousness are more varied and less characteristic. The most marked is a feeling of general weakness and extreme fatigue, which often lasts for several days, and accurately corresponds to the objective symptoms of this stage. Vague headaches, a want of clear conceptions, and general obscurity of the mental faculties are associated with this, as they are with many other conditions met with in a variety of other diseases. Eccentric pains in the extremities, and disorders of cutaneous sensibility are especially marked in those cases where the poisoning gives rise to profound functional mischief of the spinal cord. In cases which end fatally, the victims either never wake from the deep coma (sopor), or their awakening is only transitory and imperfect, and soon gives place to fresh attacks of insensibility, and more or less suddenly leads to death. The objective phenomena observed in cases of poisoning by carbonic oxide are very numerous and varied, and may be conveniently grouped, according to the organs affected, somewhat as follows :

The *external surface or skin* of those poisoned shows much congestion and redness at an early stage, particularly in the

face; the ocular conjunctivæ are injected, but the diameter of the pupils is not much affected. The color of the *mucous membranes* accessible to sight usually remains for a long while of a lively red. In the later comatose stages the skin is for the most part pale, and only becomes livid and cyanotic towards the end of life, in consequence of the disordered circulation. Many observers have also noted, during the poisoning itself, and in the sequelæ which are so often met with in these cases, a great variety of *cutaneous* affections, from simple *rubeola*, or the formation of blisters, to extensive *gangrene* and *bedsores*—symptoms which probably depend on the vaso-motor paresis. Herpetic eruptions, both simple *herpes labialis* and the so-called *herpes zoster*, have been observed as consequences of poisoning by carbonic oxide (Leudet[1]).

The *respiratory functions* are not always very prominently affected in carbonic oxide poisoning; and this is no doubt one reason why so many authors have been led to doubt the theory of a simple suffocative action of the poison. The cases in which early dyspnœa is succeeded by asphyxic convulsions, thus plainly indicating suffocation, are certainly far from common. It is far more general for the initial stages of dyspnœa to be succeeded by a comatose condition, in which sometimes it would appear as if there were no hindrance to respiration, which goes on in a regular rhythm, death occurring without any marked convulsions. But, on the other hand, there is no doubt that the rule is for convulsions to occur in the final stages of poisoning by carbonic oxide.

Siebenhaar and Lehmann[2] point out that symptoms of dyspnœa do not generally occur until after the general paresis and weakening of the cardiac activity; and they believe accordingly that this renders the suffocative theory of the action of the poison untenable. On the other hand, these authors sketch so typical a picture of death by suffocation, that it only wants to be pointed out in order to convince as to the possibility of this explanation.[3] We must indeed not expect in

[1] Archives générales. VI. Ser. tom. 5. Mai 1865. p. 513.

[2] Loc. cit. p. 41.

[3] We quote a small portion *verbatim:* "Towards the end of the attack, the breathing is in almost all cases somewhat quickened, and even seems to be tolerably energetic, and as if accomplished with great exertion (sic); but in general this rapidity of the

these cases such violent (*lit.* stormy) symptoms as occur after forcible ligature of the throat (strangulation), or after similar modes of suffocation. The gradual impoverishment of the blood as regards oxygen will be likely to bring about a similar gradual change in the functions of the respiratory centres.

All the observations made, both on men and in animals, show that the inspirations become marked by pauses which gradually grow longer, and thereby the respirations gradually acquire a forced and truly dyspnœal character, whilst, at least in the early stages, respiration is temporarily accelerated, and there is at the same time a feeling of precordial anxiety.

But besides these abnormities of respiration dependent on the nerve-centres, we sometimes get, particularly in true charcoal-vapor poisoning, palpable changes in the organs of respiration, which occur under the form of either acute *bronchitis*, *hæmoptysis*, or *pneumonia*, with or without *pleurisy*. Klebs (loc. cit.) considers these complications, often seen by him, as accidental; whilst Friedberg (loc. cit.) and others consider them to be directly dependent on the poisoning. They attribute them in part to the mixture of gases, which act as direct irritants to the lungs, etc., and partly to the disordered circulation brought about by the carbonic oxide. We must leave this controversy to be settled by more precise observations.

The objective demonstrable disorders of the *circulatory system* are confined to not very pregnant and very variable changes in the arterial pulse, which is full and quickened for a little while, but, later on, becomes gradually less powerful, and in the stage of coma can scarcely be felt. The explanation of these phenomena will be found, in part, in what has before been said as to the physiological effects. The *temperature* of the body is considerably decreased in poisoning by carbonic oxide (about 2° to 2.5° C. = 3.6° to 4.5° F., Pokrowski, loc. cit., Klebs, loc. cit.).

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in- and expiration soon passes away; the excitement gives place again to an equally tranquil condition, and the breathing in particular become less rapid and more superficial, whilst the general paresis and the condition of torpor increase; at a later stage again, there are *constantly increasing pauses in the breathing*, between which, now and then, some strong respiratory movements become visible, and finally, there follows, after one such inspiration, *that long pause* which is succeeded by death, imperceptibly and without any visible spasms or convulsions."

The disorders of the *digestive organs* are quite subordinate to the other symptoms; as a rule, there is more or less *vomiting* in the early stage. Extensive inflammation of the mucous membrane of the digestive tract, with a tendency to necrotic ulceration, has been noted in isolated cases by Ziemssen and Thomson.[1]

The occurrence of *diabetes mellitus* is of especial interest. It is a symptom now seldom wanting in cases of carbonic oxide poisoning, since first pointed out by Friedberg (loc. cit.), though as yet its real import and connection with the poisoning has not been discovered.

Senff[2] has endeavored, in a searching investigation of the pathogenesis of carbonic oxide diabetes, to establish and demonstrate that the excretion of sugar in the urine does not depend on inhibited oxygenation, since sugar injected directly into the blood of animals poisoned with carbonic oxide is burnt up, and does not pass into the urine. He has further shown that if the access of arterial blood to the liver is hindered by the ligature of the arteries concerned, there is no diabetes in these cases of poisoning by carbonic oxide; so that we may conclude with great probability that an excess of sugar is formed in the liver in this mode of poisoning. That it is really the glycogen of the liver which is concerned in this matter is also shown by the fact that the diabetes is generally absent in fasting animals, in whom it is admitted that the liver is almost entirely free from glycogen.

For the most part the *diabetes* in poisoning by carbonic oxide is associated with *albuminuria.* Both these symptoms last for a few days only at most, and disappear with the other symptoms of poisoning.

Lastly, as regards the palpable disorders of the *nervous system*, these are limited to sometimes local, sometimes general *anæsthesia* of the cutaneous surface and *paralysis* of the voluntary muscles; the latter frequently lasts much longer than the other symptoms, and may be complicated with *atrophy* of the muscles concerned.[3] *Paralysis of the involuntary muscles* of the *bladder* and of the *bowels* is often mentioned in the cases recorded.

The course and duration of poisoning by carbonic oxide natu-

[1] See *Friedberg*, loc. cit.

[2] Ueber den Diabetes bei Kohlenoxydvergiftung. Inaug.-Dissert. Dorpat. 1869.

[3] Consult *Friedberg*, loc. cit. p. 123. History of a case by *Schwartz.*

rally depend chiefly on the duration and intensity of the action of the poison. The great frequency of fatal cases depends largely on the fact that the poison almost always, except perhaps in the case of suicides, attacks persons who are asleep, and in the night-time, so that any intervention, which would have the effect of saving their lives, if timely, does not and cannot usually occur until some hours at least have elapsed, perhaps not till next day. If carbonic oxide and the gases usually associated with it are allowed to operate persistently, they bring about a fatal termination in a few hours. If the poisoned persons are more or less quickly removed from the injurious vapors, either recovery takes place after a little while, with gradual vanishing of the symptoms, or death occurs in a day or two, various symptoms persisting in the meantime. Carbonic oxide cannot therefore be reckoned amongst the very rapidly killing poisons like prussic acid.

The *corpses* of those dying from carbonic oxide poisoning *show a remarkable resistance to putrefaction*, and exhibit outwardly certain characteristic signs of the mode of death. Amongst these are broad and extensive irregularly outlined bright-red spots or patches on the anterior surface of the whole body, the color depending on the impregnation of the blood with carbonic oxide. Sometimes a darker or more violet hue is seen, particularly if the carbonic oxide has been already converted into carbonic acid, or if the gaseous mixture contained an overwhelming proportion of the latter gas. A similar rose-red coloration is often met with in the internal organs, in the muscles and serous membranes (peritoneal coat of the intestines). The changes in the blood itself are just as little constant, the characteristic cherry-red being often replaced by the commoner dark coloration of the blood often seen in corpses. The question whether these variations depend on more or less of the carbonic oxide being present does not seem settled as yet.

The demonstration of carbonic oxide in the blood itself is, however, always an easy matter, whilst the corpse is still fresh, if Hoppe-Seyler's method be adopted. For the details of this we must refer to manuals of medical jurisprudence, and to the special literature of the subject.

Next to these phenomena, authors unanimously insist on the great fulness of blood met with in the parenchymatous organs and other viscera, and on the extreme injection of all the capillary vessels brought about by the general vascular paresis. Klebs[1] observed this most particularly in the meninges and cortical portions of the brain; and found a varicose condition of the small arteries in the membranes, which usually run in a straight course in young subjects. The *muscles* and *glandular* organs (liver, kidneys, glands of stomach) are often found in a condition of advanced fatty degeneration, in consequence of molecular degeneration of the cellular elements, as has been noted also in various other kinds of poisoning (phosphorus, arsenic, etc.). This has been confirmed lately. The glandular organs mentioned often show increase of bulk (parenchymatous swelling).

Ecchymoses are found in the pleuræ, peritoneum, pericardium, and meninges. These are probably connected closely with fatty degeneration of the coats of the vessels. This parenchymatous degeneration sometimes goes on to necrotic destruction of tissues. The corpse then exhibits patches of softening (Erweichungsherde) in the brain, kidneys, and muscles. In the *lungs*, besides emphysema of the margins (no doubt due to the dyspnœa during life), there are various inflammatory conditions, which need not be discussed here in detail, since they are met with in other cases (of disease), and are elsewhere described. *The contents of the stomach are often found in the trachea and bronchi;* and this depends, as Friedberg[2] believes, not always on a post-mortem overflow from the stomach, but very often on vomiting during life, during which the diminished reflex sensibility permits these matters to invade the air-passages unhindered.

The removal of the poisoned persons out of the dangerous atmosphere must, as a matter of common sense, be the first act of our therapeutics. Generally speaking, it is best to actually move the patient into another well-ventilated room, or into the open air, but it may sometimes be necessary or even best to treat them on the spot, changing the air of the room by appropriate measures, such as opening doors and windows, etc. The further

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[1] Loc. cit. p. 458.

[2] Loc. cit. p. 86.

treatment of each case must depend on the degree and stage of the poisoning. In mild cases, this change of atmosphere may suffice to ward off danger, especially if the patient breathes well, and is conscious. But if there be much dyspnœa or a comatose condition, we must resort to energetic measures. If respiration be re-established, it must be carefully watched. *Artificial respiration* must be performed when the breathing is badly done, or in abeyance. Even if this do not eliminate the carbonic oxide from the blood—because, as we have seen, the compound of carbonic oxide, etc., with hæmoglobin is not easily got rid of—yet the induction of artificial respiration has at least this indisputable advantage, that it may possibly excite a livelier interchange of gases in the remainder of the blood which is still normal, so that a greater quantity of oxygenated blood may reach the nervous centres. We need not enlarge on the different methods of artificial respiration. Any one of them will serve the purpose. Friedberg and Ziemssen have lately strongly recommended *faradization of the phrenic nerve* and its vicinity; a proceeding which, in any case, will prove a valuable auxiliary to artificial respiration. Air might also be blown into the larynx through a catheter or œsophageal tube. When there is much cyanosis of the mucous membranes, and very dusky hue of skin, many authors recommend *venesection*, and in experiments on animals Kuehne found that, if the animal only breathed more than once a minute, recovery took place when bleeding was done, whilst similar cases not bled died.

As in other forms of asphyxia, so here also, in addition to ordinary measures, *energetic stimulation of the peripheral nerves* is often a very rational mode of treatment. The object is to excite respiration by acting in a reflex manner on the now weakened, but still living central organs of the nervous system. Such measures as sprinkling with cold water, rubbing with ice or snow, the hot iron (thermal hammer), hot shellac, etc., may be adopted, or the mucous membrane of the nose, etc., may be irritated either mechanically or chemically (ammonia, acetic acid, etc.). When, in spite of these therapeutic efforts, the threatening symptoms persist, we are advised by Kuehne, Panum, Friedberg, Traube, and others, that recent experience is strongly in favor of a *deple-*

tory transfusion of blood. A part of the poisoned blood is first removed, and a corresponding quantity of the normal defibrinated blood of a healthy man is substituted. Several successful cases of this kind are recorded, and there seems to be no valid argument against this proceeding. In dubious cases, Friedberg strongly recommends that this exchange of blood should be repeated more than once. The methods of transfusion will be dealt with elsewhere. As regards the use of *ergotin*, suggested by Klebs as an antidote, we have no practical experience up to date. Nor can we recommend it, since ergotin is not an inert substance by any means. The treatment of the complications and sequelæ of carbonic oxide poisoning belongs to the domain of general therapeutics.

CHAPTER VII.

POISONING BY CARBONIC ACID (CARBON DIOXIDE).

Although the suffocating action of concentrated carbonic acid gas has long been known, yet there has been much hesitation in calling it a "poison." Even Claude Bernard, in his "Leçons sur les effets des substances toxiques," etc., advances the opinion that this gas, innoxious in itself, can only become dangerous to animal life when it becomes accumulated, in a concentrated form, in the air-passages, and thus hinders the oxygenation of the blood. These and similar views—as, for example, that carbonic acid is in itself an innocent or indifferent gas, like hydrogen or nitrogen—have been perfectly contradicted by the experiments and researches of the last ten years; so that nowadays no one doubts the poisonous character of this gas. Yet in practical toxicology carbonic acid does not play a very prominent part. The interesting results of numerous experiments, made by the first physiologists of our times on the relations of this gas to the processes of respiration, do not very greatly increase our knowledge of this matter, and indeed, as regards the peculiar toxic effects of carbonic acid, the experimental science of our

day still fails to answer the question—"In what way does this gas kill?" Since carbonic acid only causes severe symptoms in very considerable quantities, or after a relatively long duration of exposure, we seldom have opportunities of observing cases of poisoning in human beings. When such cases do occur, they either kill so quickly that any accurate observation is impossible, or the symptoms in other cases are so slight and transient as not to admit of careful determination. Our present task will be limited to furnishing a brief and condensed sketch of the present state of our knowledge of the action of carbonic acid, referring for more minute and extended details to purely physiological literature.

Carbonic acid is a gas at the ordinary pressure of the atmosphere, and in the presence of carbonated salts it is very largely dissolved in watery fluids; by the application of higher pressures a large quantity can be condensed or compressed into distilled water. It is a weak acid, reddens litmus paper, and excites a slight, pleasant, cool, prickly or pungent sensation in mucous membranes largely supplied with nerves (such as the lips, tongue, palate, etc.).

As carbonic acid is set free from its combinations with most bases by the stronger acids of the stomach, the carbonated salts must be included with the acid. Carbonic acid seems to be absorbed most rapidly from the surface of the lungs, yet a very considerable quantity passes into the blood from the stomach and intestinal canal, from the subcutaneous connective tissue, and even from the uninjured epidermis. From the blood it is returned again to the atmosphere through the lungs, with a rapidity proportioned on the one hand to the smallness of the percentage of carbonic acid in the surrounding air, and on the other hand to the intensity of the breathing process. If the quantity of carbonic acid in the air is so great as to equalize the pressure of the gas within the blood, the gas in the blood will be retained there, and may accumulate so as to produce dangerous effects, since the gas continues to be formed within as before. Hence it comes to pass that both men and animals may be poisoned by the carbonic acid they themselves generate, provided they remain long enough in a restricted space without [ade-

quate] ventilation, although in such cases the gradually increasing deficiency of oxygen plays a very important part.

In the mode of its operation, carbonic acid undoubtedly deserves to be ranked with narcotic poisons. The most important elements in its operation are the effects it produces on the central nervous system.

Carbonic acid, according to physiologists, is one of those irritants which bring about the respiratory movements by way of the medulla oblongata. Traube[1] was the first to show this by experiments. Thiry's view[2] indeed was that carbonic acid is the only stimulus which in normal life keeps the respiratory centres in rhythmic activity. However, Pflueger[3] contradicts this view, and considers the want of oxygen to be the normal stimulus or excitor to respiration; but admits, without reserve, that carbonic acid may also act as a stimulus. Whilst, then, small quantities of carbonic acid only excite to a regular and orderly activity of the muscles of respiration, the accumulation of carbonic acid in the blood causes this stimulation to be more and more intense. In this way we get a typical attack of dyspnœa—at the beginning of the attack quickened and forced breathing, later on spasmodic inspirations with long intervals between them, till at last the respiratory centres, through the excessive stimulation—the over-excitation—become paralyzed, and thus death occurs as in suffocation. Hermann[4] remarks that this kind of respiratory paralysis, through over-stimulation of the respiratory centres, should not be identified with ordinary simple asphyxia, in which the loss of excitability of the respiratory centres is originally brought about by the deficiency of oxygen.

It is to be regretted that hitherto no experiments of any value have been made which illustrate the action of carbonic acid in animals which are under the influence of curare, and whose respiration is kept up by artificial means. We do, indeed, know that, as a rule, in poisoning by carbonic acid, respiration generally ceases before the heart stops beating. But since, from the

[1] Gesammelte Abhandlungen. I.

[2] Quoted by *Traube*.

[3] Pflueger's Archiv. I.

[4] Experimental. Toxikologie.

moment respiration comes to a stand-still, the poisonous action of carbonic acid is complicated with deficiency of oxygen, we do not know the precise share of carbonic acid in the production of the cardiac paresis.

Castell[1] and Schiffer's[2] experiments have shown that the activity of the frog's heart is only temporarily depressed by carbonic acid, provided the exposure is not too protracted; indeed the activity is sometimes temporarily increased. If the circulation is carefully watched in mammals poisoned with carbonic acid, the appearances are the same as in poisoning brought about by common suffocation (carbon compounds, deficiency of oxygen). The symptoms consist in retardation or slowing of the pulse, and, at the beginning, in a very considerable elevation of the arterial blood-pressure. In later stages this is again suddenly depressed. Traube considers that the slowing of the pulse depends on a central irritation of the vagus—the varying levels of the blood-pressure are brought about by irritation and perhaps paralysis of the vascular nerves. But the locality of vaso-motor stimulation is not yet accurately determined. Traube's opinion that the stimulation occurs in the vaso-motor centre of the medulla oblongata seems contradicted by the fact that this increase of blood-pressure occurs in animals whose cervical cord has been cut across or divided before the poisoning.

A great many symptoms show that carbonic acid affects the functions of other nerve-centres. These have been verified in both men and animals during the narcosis induced by carbonic acid. Its action on the cerebrum is shown sometimes by men falling into a condition resembling the drunkenness of "jolly topers," with cheerful garrulity and pleasant hallucinations, whilst the occasional occurrence of tetanic convulsions in animals indicates that the spinal cord becomes affected.

Carbonic acid is ranked with those poisons to whose toxic action the system becomes gradually accustomed (so-called "law of tolerance"), because it has been observed that people who remain in air rich in carbonic acid gradually become less sensitive to the action of this injurious agent.

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and [2] Quoted by *Hermann*, Exper. Toxikol.

The local effects of carbonic acid are, it would seem most probable, the consequences of direct irritation or stimulation of the nerves of the part to which it has been applied. The reddening of the skin, the feeling of warmth, the total local anæsthesia which finally occurs, and the increased activity of the secreting organs (sweat-glands, salivary glands) can all be explained on this hypothesis.

The circumstances which give rise to poisoning by carbonic acid are very numerous and varied.

There are many localities in which this poisonous gas escapes forcibly from the surface of the soil, and accumulates either in caverns and grottoes, or sometimes fills the whole of a valley in such dense quantities as to cause both men and animals who come there to succumb at once to its influence. Amongst such places are the well-known *Grotto del Cane*, or Dog's Cavern, of Pozzuoli, near Naples, the Lake of Laach, in Switzerland, and its vicinity, and others near Marienbad and Pyrmont, the poison-valley of Java, and other localities, more particularly in the neighborhood of volcanoes.[1] Large quantities of carbonic acid may be found in charcoal works (in dull weather, fogs, etc.), mines, deep wells, wine and beer cellars, in which the liquors named undergo fermentation, in vats, cellars, and in small, badly-ventilated rooms and houses where many men live together, or remain long in one room. It has also been mentioned under carbonic oxide that carbonic acid is one of the products of combustion. In all the cases mentioned the poison is breathed in or inhaled by the air-passages. It is far less usual to meet with cases of poisoning due to the ingestion of beverages rich in carbonic acid (sparkling wines, soda-water, etc.) or through the medicinal application of carbonic acid as a local anæsthetic.[2]

We may consider as mild cases of poisoning by carbonic acid those attacks which often occur to those who have been long in rooms which are overcrowded and badly ventilated. These consist of headache, noises in the ears, with occasionally giddiness, nausea, and syncope. As a rule, these symptoms generally van-

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[1] Consult, for details of these, *Hasselt* and *Husemann*, loc. cit.

[2] See *Husemann*, *Eulenberg* (loc. cit.), for details.

ish, without any particular after-consequences, on removal from the atmosphere which induced them. If concentrated mixtures of carbonic acid be inhaled, violent symptoms of the character of dyspnœa occur. Those poisoned fall senseless to the ground, and generally succumb rapidly with symptoms of suffocation. It seems unnecessary to enter more into detail as to symptoms, because these are absolutely identical with those met with in asphyxia and suffocation. The treatment of cases of carbonic acid poisoning is also identical with that proper in asphyxia.

CHAPTER VIII.

POISONING BY BISULPHIDE OF CARBON.

The bisulphide of carbon (CS_2) owes its practical importance in toxicology entirely to its technical uses in the manufacture of India-rubber and of articles made from this. On account of its low boiling point (47° to 48° C.=116.6° to 118.4° F.) and consequent great volatility, as well as on account of its action upon animals, this poison, considered from a theoretical point of view, presents many points of analogy with the volatile anæsthetics. It is a liquid at ordinary temperatures, and its evaporation develops a good deal of cold, with the formation of characteristic strong-smelling vapor, which is specifically heavier than atmospheric air, and if fired burns with a blue flame (generating sulphurous acid). This oily, highly refractive, and generally pale-yellow fluid has a specific gravity of 1.27, and is not miscible with water, but mixes readily with alcohol, ether, chloroform, etc., etc.

Bisulphide of carbon most easily finds its way into the animal economy by the lungs, through whose capillaries the vapor of this substance, mingling easily with the air inspired, is absorbed in considerable quantity into the general mass of the blood. In what way, or if at all, it is absorbed by other organs is not yet known. Like ether and chloroform, the bisulphide of carbon, on account of its rapid evaporation and the loss of temperature thus induced, acts locally as a powerful irritant. Its prolonged action on the skin is that of a local anæsthetic.

As regards its true action on the system, and the way and manner of its elimination, there are as yet no trustworthy experiments or observations. It is, however, known that in those who have long breathed an atmosphere of bisulphide of carbon, the urine acquires the smell of this substance.

Hermann[1] has found that when bisulphide of carbon is mixed with blood, the red corpuscles become dissolved. Our own observation shows the same result when fluid bisulphide of carbon is mixed with frog's blood. But the nuclei of the red corpuscles are left undissolved. It has not, however, as yet been determined whether this solvent power of the poison is displayed in the same way in the blood circulating in a living animal. According to Hermann's[2] and Hirt's[3] experiments, which we ourselves have lately repeated with similar results, bisulphide of carbon acts upon frogs just like chloroform, ether, and alcohol, by simply paralyzing them. If the animals thus affected with general paralysis are quickly removed from the poisonous atmosphere, they perfectly recover after a little while. The action of the heart, at first feeble, after a while ceases entirely. Hirt found that the heart of a frog, removed from the body and put into an atmosphere of bisulphide of carbon, was perfectly paralyzed after some twelve to fifteen minutes, though at first its pulsations were quickened considerably.

The experiments also of Delpech,[4] Cloez,[5] and Hirt on mammals do not exhibit any remarkable difference between the action of bisulphide of carbon and that of other volatile anæsthetics. Hirt has studied the changes in respiration and circulation. The former, after being considerably quickened at first, is brought to a stand-still after a few minutes—this pause, however, only lasts about sixteen seconds, and then gives place again to very rapid breathing, even when no more of the poison is exhibited. Section of the vagus nerves only causes a later and more gradual development of these phenomena. Hirt draws the con-

[1] Archiv für Anat. und Physiologie. 1866.

[2] Handbuch d. exp. Toxikol. [3] Die Krankheit d. Arbeiter. I. 2.

[4] Nouvelles recherches sur l'intoxication spéciale, que determine le sulfure de carbone. Paris. 1860.

[5] Gazette des hôpitaux. 1866.

clusion that the poison acts on the pulmonary vagus fibres as a stimulant, but on the centres for respiration first as a stimulant, and then as a paralyzer. As regards the circulation in mammals, Hirt found only a rise of blood-pressure, lasting for a few seconds, amounting to about 50–70 mm. of mercury in dogs and cats, which he considered as the effect of vaso-motor excitement. The disordered respiratory functions precluded any further trustworthy observations on blood-pressure.

So far we are warranted in concluding that the action of bisulphide of carbon does not essentially differ from that of other anæsthetics. But the present state of our knowledge sheds no light on the obscurity which veils the origin of those symptoms which are observed in practice as the result of chronic poisoning by bisulphide of carbon. Delpech has himself, with some probability, compared them to alcoholism, and, indeed, the study of his cases and communications compels us to draw the conclusion, that the long-continued action of this poison brings about in the central nervous system degenerative changes which are similar to those induced by chronic alcoholism.

Cases of acute poisoning by bisulphide of carbon are rare, and must be attributed to similar causes with the more chronic forms. There have been accidents in the factories and workrooms, of which we shall presently speak, through the breaking of large jars of the liquid, etc. Chronic poisoning by bisulphide of carbon generally attacks people, as has been said, employed in the manufacture of India-rubber—more particularly the red variety, used for the little toy balloons filled with hydrogen, for condoms, etc., etc. To prepare it, the caoutchouc is steeped in a mixture of bisulphide of carbon and sulphuric chloride (mostly in the proportion of 99 to 1), so that the workpeople, besides breathing in the poisonous gas, are also frequently bringing their hands in contact with the fluid. We owe the first accurate account of these circumstances to Delpech, who made careful investigations on the subject in Paris and its vicinity. Considering the great extent to which India-rubber is manufactured, we cannot help, even at the outset, expressing surprise that very few other countries or places have furnished us with accounts similar to those of Delpech. Hirt expressly says that in a large

factory in Hamburgh which he visited, only about two in a thousand of the workpeople suffered from any symptoms of poisoning. But careful reading and consideration of Delpech's report give us satisfactory reasons for this. All the French cases occurred in small establishments, in close, badly-ventilated localities, whilst in the larger factories great care was taken to get good ventilation. In the Paris establishments there was often such a quantity of the bisulphide of carbon vapor, that the approximation of a light caused blue flames and a slight explosion. It is also noteworthy, that, owing to its specific weight, the poisonous vapor formed a dense layer on the floors of the workrooms.

The suspicion that the vapors of bisulphide of carbon were only partly to blame, and that the nasty smelling chloride of sulphur by its fumes might have a share in the mischief, Delpech, on the ground of experiments, sets quite on one side. Chloride of sulphur has a very high boiling point (138° C. = 280° F.), and the scanty fumes given off at ordinary temperatures, though intensely nasty smelling, do not injuriously affect either men or animals.

On the ground of many careful experiments with negative results, Delpech combats the notion that it was possible that the vapors of both substances might combine into a compound with a specific action. We must, therefore, conclude that bisulphide of carbon is the sole cause of the symptoms of poisoning in question.

Age, sex, individuality, and constitution, all very considerably modify the susceptibility of those exposed to the poisonous action of this substance. In Paris it is thought that the habitually intemperate are particularly exposed to danger from bisulphide of carbon. Besides Delpech's twenty-four cases of chronic poisoning (of which three were also acute), there have lately been isolated cases published by Fries and Bernhardt. The symptoms of acute poisoning in human beings are not very accurately described. In the cases given by Delpech there was temporary, but complete loss of consciousness.

The accounts given of chronic poisoning furnish a very characteristic picture, and so far as Delpech's cases go, the type is

a constant one. The workpeople may live for weeks or even months in the poisonous atmosphere, before the severe symptoms occur, but, as a rule, they experience some inconvenience the first time they remain long in the bad air—the attacks repeat themselves daily, and gradually get worse and worse. The chief thing is an intense, oppressive headache, spreading from the root of the nose towards both temples, with a feeling of giddiness and of intoxication (ivresse), of which the workpeople complain, when they go home in the evening. In several cases it was noticed that a more or less marked stage of excitement now developed itself. These people became remarkably lively, chatty, and excitable, and their sexual passions became greatly excited; sometimes their appetite for food also became insatiable. According to Delpech, however, this stage of excitement is not only sometimes absent, but almost always intermingled with many symptoms of depression. All the patients, without exception, complained very quickly of an evident loss of muscular strength. In later stages, many were troubled with remarkable loss of memory. They fell into a deep apathy, could not think, strove in vain for the words they wanted, and spoke with a stammering and almost paralyzed tongue. Their mental condition was strikingly obtuse, the energy of the will greatly depressed. With this were associated many anomalous symptoms in the sensorial and motor domains of the nervous system. The faculty of vision vanished, beginning with a slight obscuration of the field of sight, and going on to complete inability to recognize small objects. Hearing also was greatly impaired, and a great many complained also of a persistent and troublesome ringing in the ears. Taste and smell were generally intact, but it was very common, particularly in the early stages, to hear the complaint that all they ate appeared to have the taste or smell of the bisulphide of carbon. The loss of muscular power was generally most noticeable in the lower extremities, and in the severer cases there was a considerable amount of paresis, so that the patients could only walk with the help of a pair of crutches, or two sticks. All movements were accompanied with a feeling of great fatigue. As regards sensation, there were severe lancinating pains in various groups of muscles, increased by pressure,

—formication,—anæsthesia of the soles of the feet, and almost constant complaints of a feeling of icy coldness in the whole of the lower half of the body; and Delpech considers that the latter symptom very probably depends on the direct action of the poisonous gas on the lower parts of the body, which were constantly exposed to the thick atmosphere of the bisulphide of carbon vapors on the floor.

Cramps and fibrillary contractions of various muscles and muscular groups were very seldom absent. Severe cramps in the calves very commonly harassed the patients during the night, and Delpech observed general epileptiform convulsions in several cases. The stiffness, numbness, and anæsthesia of the fingers and hands are clearly to be regarded as the local action of the poisonous fluid to which the hands were exposed.

In the domain of what are called the vegetative functions the anomalies are less uniform. Apart from the rarer cases in which the appetite is enormous, digestion is almost always more or less impaired. A good many of the workpeople suffer from vomiting, others from severe and very often repeated attacks of colic. In the early stages of poisoning, diarrhœa and constipation alternate with one another; in the later stages, the latter predominates, and is generally associated with troublesome flatulence. The intestinal gases are very strongly impregnated with the unpleasant smell of the bisulphide of carbon. The urine also, which is generally in normal quantity, though passed with a painful sensation of scalding, exhibits the same smell, but contains neither albumen nor sugar.

The organs of circulation and respiration exhibit no special disorders in their action.

The sexual passion, which is increased at first, rapidly declines at a later stage, and finally there is complete moral and physical impotence, with decrease of the size of the testicles.

In women who work long in the India-rubber factories, menstruation always takes place prematurely, and is more profuse than it should be. They never have a child, and their sexual appetite becomes entirely lost.

Youths who are exposed during pubescence to the influence of the poisonous gas, never develop properly. As regards the

general condition of those poisoned, it has been noticed that a good many suffer from a febrile movement at night. Sleep is disturbed with bad dreams, generally associated with nightmare (Alpdrücken), and sometimes prevented by pains and cramps in the muscles.

When the poisoning is protracted, the patients lose a good deal of flesh, but no special atrophy of muscles has been met with.

Notwithstanding the severity of many of these symptoms, and the great general weakness associated with them, an immediate fatal termination is very seldom a consequence. It is very remarkable, that when the patients, after a longer or shorter respite from their injurious toil, have gained some benefit in hospital, they almost always return to their work, the injurious effects of which most certainly destroy both their health and their success in life. This return to the work explains the fact that many of these cases of well-marked chronic poisoning are protracted through several years—and as the organism does not seem to get much accustomed to these noxious fumes, the symptoms last, with more or less intensity, till the patient finally resolves to abjure forever this deleterious employment.

Delpech, however, remarks that a complete restoration to health and strength, after these symptoms, is quite a rare thing. As a rule, the patients, all their life long, show marked traces of their past sufferings. They exhibit constant depression and a melancholy mood, sometimes complete apathy (Indifferentismus), and the intellectual faculties, like the power of the will and of voluntary movements, continue to be impaired and diminished. In some cases the chronic poisoning ends in some definite psychosis—and a good many in all probability die without our having any very definite idea of the precise mode of death.

The treatment of these sad cases naturally resolves itself in great part into the fulfilment of the causal indication. Indeed, in the worst cases, one generally sees a considerable improvement as soon as ever the patient can be removed from the injurious atmosphere. The use of tonics, and of means to restore the strength and to combat the almost universally present disorders of digestion, appears to be indicated by the dictates of common

sense. In this way, if the cases are not too chronic, the nervous disorders, the paresis, pains, and disorders of sensation will almost perfectly vanish without special treatment, although some general weakness and deficiency will probably remain.

Delpech believes that he attained more than usual success by the administration of small doses of phosphorus (daily from one sixty-fifth to one-thirteenth of a grain) in pills—the use of which he believes to have removed actual impotence and paresis, etc. He guards himself, however, from rashness in concluding that this was definitely due to the phosphorus, but thinks the results justify a further trial of the remedy. The use of phosphorus is generally followed at first by severe diarrhœa, but after two or three doses this becomes less severe and does not return.

Fries has pointed out that partial or complete paresis of voluntary muscles may be benefited by the use of the constant current.

CHAPTER IX.

POISONING BY SULPHURETTED HYDROGEN (HYDROTHIONÆMIA).

Sulphuretted hydrogen (hydrogenium sulfuratum, Wasserstoffsulfid, hydrothion, H_2S) is at ordinary temperatures a colorless gas, with an intense smell of rotten eggs, and it is absorbed by water with great facility, communicating to the solution the characteristic smell of the gas, a well-marked acid reaction, and an unpleasant taste (solution of hydrogen sulphide of chemists; natural sulphur waters).

Both the gas and its solution concern toxicologists, inasmuch as the poison can be absorbed by animal bodies under both forms. The gas diffuses itself very readily into the blood through the lungs, and by the mucous membrane of the digestive tract, both in warm- and cold-blooded animals, including human beings, and may also pass into the circulation through the skin without any wound of this covering. This absorption by the skin is proved as regards frogs by the experiments of Kaufmann and Rosen-

thal;[1] and as regards mammals, by Amelung and Falck.[2] The subjects of experiments exhibited manifest symptoms of poisoning when only the outer integuments were exposed either to the gas or to its solution.

Many experiments of Nysten,[3] Orfila,[4] Amelung and Falck (loc. cit.), Eulenberg,[5] Claude Bernard,[6] Demarquay,[7] Kaufmann and Rosenthal (loc. cit.), and others, have also taught us that the gas may be injected in pretty considerable quantities immediately into the veins or arteries of warm-blooded animals without giving rise to gaseous embola or other mechanical disturbances of the circulation. It appears to be absorbed by the blood immediately, and its deleterious action suddenly manifests itself. This takes place also, though less rapidly, when sulphuretted hydrogen gas or its watery solution is injected into the subcutaneous connective tissue or into the serous cavities of animals. Although the poison may be thus absorbed into the blood through various channels, its elimination from the blood occurs principally through the lungs, for the air expired from the lungs of men and animals poisoned with this gas blackens paper previously prepared with solution of plumbic acetate and moistened. In several cases of hydrothionæmia in human beings sulphuretted hydrogen has also been detected in the urine.

This was the case in three instances (one detailed by Betz[8] and two by Emminghaus[9]) of so-called self-infection by sulphide of hydrogen (spontaneous development of the gas in the body (see farther on, p. 491), whilst Senator in a similar case found the urine free from this poison.[10]

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[1] Archiv f. Anat. u. Physiol. 1865. p. 659–675.

[2] Deutsche Klinik. Jahrgang 1864, Nos. 39–41. 1865, Nos. 17–33.

[3] Recherches de Physiologie et de Chimie pathologiques. Paris. 1811. Article VII. p. 114–130.

[4] Toxikologie, übersetzt v. *Hermbstaedt.* Berlin. 1818. p. 117.

[5] Die Lehre von den schädlichen und giftigen Gasen, etc. Braunschweig. 1865.

[6] Innocuité de l'hydrogène sulfuré, etc.—Gazette des hôpitaux. 1857. No. 139.

[7] Note sur l'hydrogène sulfuré, etc. Comptes rendus. Tom. 60. 1865. pp. 724–727.

[8] Ueber Hydrothion-Ammoniämie. Memorabilien. 1864. p. 146.

[9] Two Cases of Perforations in the Digestive Canal, with Sulphuretted Hydrogen in the Urine. Berlin. klin. Wochens. 1872. Nos. 40 and 41.

[10] Ueber einen Fall von Hydrothionämie und über Selbstinfection durch abnorme Verdauungsvorgänge.

In order to understand the working of this poison, it is naturally of the first importance that we should try to discover its action on the blood itself. Before any answer to this question was sought by way of experiment, all sorts of hypotheses were invented. For a long time it was held that the iron in the blood was precipitated as sulphide of iron. This opinion, entertained formerly by Liebig, was based on the dark color of the blood in cases of poisoning by hydrogen sulphide. Robbed of its iron, the blood could no longer be oxygenated, and thus death occurred through suffocation. Meanwhile, no one ever obtained the sulphide of iron from blood in cases of poisoning by sulphuretted hydrogen. We owe more exact investigations into the changes produced in the blood by sulphuretted hydrogen to Hoppe-Seyler,[1] Kaufmann and Rosenthal (loc. cit.), Diakonow,[2] and Preyer.[3] The alteration in the blood of frogs when they have been long exposed to the influence of sulphuretted hydrogen is very remarkable. The whole mass of blood in these animals assumes a smutty, vivid green color, and nearly all the blood-corpuscles are destroyed.

In warm-blooded animals the decomposition of the blood can never advance so far, because their more delicate nervous centres are roused into activity by far less considerable alterations in the blood. We therefore find that the blood of men or animals thus poisoned only assumes a darker tint than normal, and already in life the difference in color between arterial and venous blood has almost disappeared. But the characteristic absorption bands of oxyhæmoglobin can still invariably be recognized by the spectroscope. But when blood withdrawn from the body of men or animals is mixed with a large quantity of this gas, the complete disintegration occurs just as in frogs, and a similar smutty green color is produced, with simultaneous separation of sulphur and of albuminous compounds.

This decomposition is exhibited in a striking manner only by oxygenated blood or solutions of hæmoglobin, so that it is most

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[1] Zeitschrift für praktische Chemie von *Huebner*. 1865. p. 514.—Medicinisch-chemische Untersuchungen. I. 1866. p. 151.

[2] *Hoppe-Seyler*, Medicinisch-chemische Untersuchungen. II. 1867. p. 251.

[3] Die Blutkrystalle. Jena. 1871. p. 158.

probable that it is due to an alteration of oxyhæmoglobin. Both Hoppe-Seyler and Preyer admit that a new chemical compound of blood-pigment and sulphur is found in this decomposition, to which Preyer gives the name "hæmathion." Diakonow has also (loc. cit.) discovered some very interesting relations between the sulphide of hydrogen and the inorganic salts of the blood. The carbonated alkalies and alkaline phosphates may become converted into sulphides of the alkalies when sulphuretted hydrogen is mixed with their watery solutions (and they are in solution in the blood). But if atmospheric air or oxygen also be present, they have a great inclination or tendency to be converted into compounds of sulphurous or even sulphuric acid. Now, if a similar reaction goes on in the blood, it is clear that the oxygen of the oxyhæmoglobin would thus be diverted from its proper purposes, and appropriated by these salts.

But since, as we shall see, the symptoms of poisoning by sulphuretted hydrogen are exactly identical with those of suffocation, the facts above mentioned are valuable as furnishing us with some aid toward explaining the symptoms met with in such cases.

However, the present state of our scientific knowledge leaves us still in doubt whether the deficiency of oxygen which results in suffocation is brought about by the destruction of oxyhæmoglobin, and the formation of hæmathion, or by the action of the poison on the salts contained in the serum of the blood; or whether, very likely, the sulphuretted hydrogen, in and by itself, irrespective of any chemical changes in the blood, has a directly deleterious influence on the mechanism of respiration. It has already been shown that the blood of men and animals thus poisoned always shows a pretty fair proportion of oxygen. It is, therefore, not very probable that, in the living body, there can be anything like that complete destruction of the blood-coloring which occurs in oxygenated blood exposed to sulphuretted hydrogen outside the body, or that this can be the true cause of the symptoms of poisoning we observe in the living. Diakonow's discovery of the change of the salts of the blood-plasma into alkaline sulphides, and their subsequent oxidation into sulphites and sulphates at the expense of the oxygen of the

hæmoglobin, might with more probability be regarded as the cause of the dyspnœa characteristic of this kind of poisoning, only that at present the question remains undecided, whether the sulphide of hydrogen be not a specific poison affecting respiration.

The opinion entertained by Claude Bernard (loc. cit.), and adopted by Hoppe-Seyler, that hydrogen sulphide is not injurious when introduced into the veins, but kills rapidly when introduced into the arteries of a living animal, has not been confirmed.

Nor have any satisfactory proofs been afforded of the opinion formerly held by Hoppe-Seyler (loc. cit.), that the sulphur, which was set free or precipitated in the blood in cases of poisoning by sulphuretted hydrogen, brought about death by forming capillary embolisms in the lungs.

The experiments of Kaufmann and Rosenthal as to the injurious effects of this poison on the cardiac movements are more satisfactory. The symptoms observed consist in a primary retardation of the pulse, and diminished blood-pressure dependent on central irritation of the vagus nerve, and the consequent gradual but steady decrease of the activity of the heart, ending in diastolic stoppage of this organ; and they agree closely enough with the disorders of the circulation observed after poisoning with carbonic oxide or simple suffocation. All the remaining symptoms, too—particularly the convulsions preceding death, and the disordered functions of the brain—find their simplest explanation when regarded as symptoms of suffocation.

Authors generally[1] agree in considering sulphuretted hydrogen as one of the most powerful and deadly poisons. As a matter of fact fatal poisonings by this gas are not uncommon, and the frequently violent and rapid course of such cases would seem to amply justify such a classification. However, it must not be forgotten that in ordinary life many men from day to day inhale considerable quantities of this gas without suffering any ill effects.

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[1] *Christison, R.*, Treatise on Poisons, German translation, Weimar, 1831, p. 819, calls sulphuretted hydrogen "the most injurious gas known." See also *v. Hasselt-Henkel*, loc. cit. p. 376, and *Husemann*, loc. cit. p. 749.

We refer to laborers in dung-pits, cesspools, privies, chemical laboratories, etc. The Parisian *vidangeurs* are said to generally enjoy very good health, and during the cholera epidemic in Paris in 1832 it appears that they suffered from that disease even less than other people.[1]

Besides this, it is to be considered that in most of the fatal cases which have occurred of poisoning by sulphuretted hydrogen, very enormous quantities of this gas have been required to kill, whilst there has simultaneously been an almost total *deprivation of atmospheric air*. We cannot, therefore, rank sulphuretted hydrogen in quite the same class with prussic acid and similar poisons, which kill in almost minimal doses, and we cannot call it one of the strongest poisons. The fatal cases are far from numerous, if we consider the number of occasions on which workingmen are exposed to the action of this gas. It is, however, a striking fact that when one dies thus it is common for several to perish together, generally from want of caution, and from imprudent attempts to rescue the first victim, fresh victims falling a sacrifice to the fate of the first.

Numerous cases of this kind are recorded, as that of Casper,[2] where six healthy men perished in a tan-pit, through a mixture of gases strongly impregnated with sulphuretted hydrogen.

Amongst the numerous conditions and circumstances giving rise to poisoning by sulphuretted hydrogen, the following deserve especial notice:

In a few localities only, very close to large volcanoes (Solfatara of Puzzuoli, near Naples, and some parts of Sicily), the sulphuretted hydrogen formed in the interior of the earth, and escaping in dense vapors from its crust, may give rise to cases of poisoning. Such cases are more commonly noted through the use of mineral waters strongly impregnated with the gas, although severe cases of poisoning from this cause also are not very common. As a rule, the sulphuretted hydrogen found now and again in the air is due to the decomposition of animal and vegetable substances. In this way, as Fr. Daniell[3] has shown,

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[1] *v. Hasselt*, loc. cit. p. 380.

[2] Handbuch der gerichtl. Medicin. II. p. 598.

[3] Philosoph. Mag. and Journal. III. Ser. July, 1841. Consult also the article "Air" in *Tardieu's* Dictionnaire d'hygiène publique et de salubrité. 2. Ed. Paris, 1862.

enormous quantities of this gas are generated on the coasts of Africa, when the large rivers debouch into the sea, by the decomposition of the sulphates of the sea-waters by the great quantity of decomposing vegetable substances which the rivers are carrying towards the sea. These cause numerous cases of poisoning amongst seafaring people.

The putrid decomposition of animal substances is the richest source for the generation of hydrothion gas, and this is the most frequent cause of cases of poisoning, since these sources of danger are most naturally to be found in the immediate vicinity of human habitations.

And, although the sulphuretted hydrogen in these cases is almost without exception mingled with other gaseous products of putrefaction, such as carbonic acid, ammonia, etc., yet experience has taught us that it is almost exclusively the sulphuretted hydrogen which constitutes the poisonous and dangerous part of the mixed gases. The most important substance (Muttersubstanz) for generating sulphuretted hydrogen in sewers and cesspools, is human ordure. For, although urine in decomposing may give rise to the formation of this gas, by the decomposition of its sulphates, yet the mixture of gases found in putrid urine owes its chief properties to ammoniacal gas. But when fæces are present in large quantities, the remains of undigested albuminous bodies, such as gelatine, etc., afford a material richly capable of furnishing enormous quantities of sulphuretted hydrogen.

Accordingly, the quantity of this gas present in the gases given off from privies, etc., will greatly depend on the richness or poverty of the albuminous constituents of the food. The closets and cesspools used entirely by the proletariat, like those of convents, will therefore be far less dangerous to the scavengers (vidangeurs) than those of the upper classes, who take a superior diet, more rich in albuminous compounds.[1]

But many other kinds of animal substances afford materials for the generation of sulphuretted hydrogen—pits in which animal excreta are collected, flayers' and knackers' yards, badly regulated churchyards, sewers, dissecting-rooms, dirty slaughter-houses, where small fragments of meat, etc., are allowed to de-

[1] *v. Eulenberg*, loc. cit.

compose, cesspools, and other similar places belong to this category. In special cases it will depend entirely on the density of the accumulations of the gas as to how far and in what degree it gives rise to cases of poisoning. In this category we must also include those cases where drinking-water impregnated with sulphuretted hydrogen has led to cases of poisoning.[1]

In the present state of our knowledge, we can only say that it is supposed that under some circumstances the living body may be self-infected by the generation within itself of sulphuretted hydrogen, "self-poisoning," as it has been termed. The number of recorded cases of this kind is very small, and the necessary conditions for their occurrence are as yet little known.

The painstaking researches of Planer[2] tend to show that in normal digestion the gases which are generated contain very little sulphuretted hydrogen, which never exceeds one per cent. of the whole quantity. In the intestines of herbivora, or of men fed exclusively on a vegetable diet, no trace of sulphuretted hydrogen is found. This originates chiefly in flesh diet, in the lower portions of the large intestine. Abnormal development of gases, and hence generation of sulphuretted hydrogen, occurs in the stomach when its free acids are neutralized. That the bile is not the original cause of the development of this gas is certain from the fact that it does not occur with a vegetable diet—a fact which also shows that we are justified in reckoning the albumen compounds as the source of this gas (H_2S), and that animal albumen is of especial importance for generating sulphuretted hydrogen.

The occasions which may give rise to self-poisoning by the generation of this gas in the digestive canal may originate from within, especially in certain forms of chronic gastric disorders, in which very probably the free acids of the gastric juice are suppressed, in consequence of abnormal processes of fermentation. Very likely this was partially so in the cases detailed by Betz (loc. cit.), whilst Senator (loc. cit.) places the generation of gas in the cæcum. In the cases of "self-poisoning" lately observed by Emminghaus (loc. cit.) there were several perforations of the digestive canal, and these had led to putrid decomposition of the fæcal matters, and to suppuration.

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[1] See *Th. Clemens*, on an epidemic of boils, originating in the use of a sulphuretted well-water. Zeitschrift f. rat. Medicin, von Henle und Pfeufer. VIII. 1849. p. 215.

[2] The Gases of the Intestinal Canal, and their Relations to the Blood. Wiener Sitzgs.-Ber. Mat.-Phys. Kl. XLIV. 1860. p. 307.

According to Biermer,[1] large quantities of sulphuretted hydrogen may be present in the fluid exudations of pleurisy with pneumo-thorax, and may perhaps lead to self-poisoning, and this gas may also frequently be demonstrated in the sputa of tuberculous patients, and of those who suffer from bronchoblennorrhœa. The poisonous gas may thus be absorbed in self-poisoning, either from the mucous membranes of the gastro-intestinal tract, from serous membranes, or from suppurating surfaces and cavities.

Many kinds of factories and works furnish a number of opportunities of poisoning by sulphuretted hydrogen; in these the workpeople find themselves in a more or less dense atmosphere of sulphuretted hydrogen, either only very occasionally and by accident, or sometimes almost constantly.

Eulenberg (loc. cit.), in his monograph on Injurious Gases, has very carefully examined this question, and from his collection we select the following:

The chief trades and occupations which are exposed to sulphuretted hydrogen are:

a. The *catgut makers.* In the process of steeping the fresh sheep's intestines, large quantities of offensive gas, containing much sulphuretted hydrogen, escape into the air.

b. The *tanners' yards.* In this trade the occasional use of the so-called "gas lime" for the skins, containing, as it does, calcium sulphide, develops large quantities of sulphuretted hydrogen when acid decoction of tan is added. Dangerous cases of poisoning are thus caused. The same thing may occur in the preparation of *Morocco* leather (Saffiangerberei), in which the so called "rusma," a mixture of sulphide of arsenic and lime, comes into use to free the skin from hair. Here again the acid decoction of tan generates great quantities of gas.

c. In the process of *flax steeping*, cases of poisoning by hydrogen sulphide occur. In this the flax is steeped under water till the parts of the flax which are not useful have decomposed, and thus the generation of sulphuretted hydrogen is unavoidable.

d. Similar processes are employed in the manufacture of *sugar* and *starches.* In the sugar manufacture it is more particularly the so-called "revivification" (Wiederleben), or purifying of the animal charcoal which has been once used for filtration, which gives rise to so much generation of sulphuretted hydrogen, when this is done by the so-called "moist fermentation," which leads to the putrefaction

[1] Ueber Pneumothorax. Schweitz. Zeitschr. 1863.

of the albuminous bodies retained by the charcoal; also when much blood is used in the sugar-houses.

e. The so-called "*wash*" (Schlempe) or residuum of the molasses which has been treated by the *distillers* with sulphuric acid, develops, by keeping, very large quantities of sulphuretted hydrogen gas, which may easily lead to accidental poisoning, if there be any want of caution.

f. In the same way, the *steeping water* of the brewers, in which barley has been steeped for the purposes of malting, will generate sulphuretted hydrogen if allowed to stand long.

Still more frequent opportunities of poisoning by the sulphide of hydrogen arise in chemical works of various kinds. First, we have the generation of the gas from sulphide of iron with sulphuric acid in the laboratory, which is often far too carelessly undertaken and frequently gives rise to accidents. Of chemical works, the most notable are the ammonia works, in which ammonia and its salts are made from urine and from the gas-tar liquor (ammonia water) of the gas-works. But especial mention must be made of the manufacture of coal-gas by dry distillation of bituminous coals (Blätterschiefer), and of the sulphuring of India-rubber in the India-rubber factories.

It is especially incumbent on medical men, who are much concerned in factories of various kinds, to acquaint themselves with the injurious products of the various manufactures.

Against the formerly prevalent opinion, that the so-called "miners' sickness," which often attacks those employed in the shafts of mines in which blasting goes on — causing sudden symptoms of syncope, etc., etc., was due to the development of sulphuretted hydrogen from the gunpowder used, very weighty objections have lately been raised. In particular, Poleck[1] has shown that the quantity of hydrogen sulphide actually present in the mine is too small to be quantitatively determined, and is a continually diminishing quantity. In the same way it has never been demonstrated satisfactorily that the gases, which are sometimes found in tunnels and other underground places, and which lead to accidents when there is but little access of air, are really injurious from containing sulphuretted hydrogen.

[1] Die chemische Natur der Minengase und ihre Beziehung zur Minenkrankheit. Berlin. 1867.

If the system be exposed to a large quantity of this poisonous gas all at once, the symptoms and course of poisoning by sulphuretted hydrogen will not unnaturally differ very materially from the effects of smaller doses of the poison, operating repeatedly and for a longer time. Accordingly, it is generally very material whether, and in what quantities, the access of atmospheric air be possible.

Acute and quickly terminating cases of poisoning are almost without exception the result of direct breathing in of the poison, and it would seem, under some circumstances, that a very few whiffs of a thick atmosphere of sulphuretted hydrogen are sufficient to cause death to human beings. In the chronic cases, either of "self-poisoning" or of poisoning by drinking-water, smaller quantities of the poison, during a long period, find access to the blood, through mucous or serous membranes.

The quantities necessary to kill, or to produce dangerous symptoms, in gaseous mixtures, have not, as may be supposed, been quantitatively determined, with any degree of accuracy, as regards human beings. Hence, we abstain from giving any figures on this subject.

Breathing a mixture containing a medium quantity of this gas, even for a very short time, produces a condition closely akin to common nausea: a general feeling of weakness with headache, inclination to be sick, with characteristically smelling eructations, vomiting, and sometimes colic and diarrhœa. With the exception of the smell of the eructations or vomit—and this is not invariably present—the symptoms present nothing characteristic or pathognomonic, and in the course of a few hours health is generally perfectly restored. On the other hand, the most severe symptoms occur when large quantities of the poisonous gas are breathed in all at once. It is by no means rare for men thus poisoned to fall to the ground with a cry as if struck by lightning. This worst form of poisoning has been observed, for the most part, where persons have been engaged in sewers or drains which have not been opened for a long time. In less severe cases, the person attacked feels a quickly increasing sense of weakness, which goes on to syncope, and after a few minutes he becomes unconscious. The breathing, quickened at

first, becomes gradually slower and more difficult, and acquires the character of true dyspnœa. The pulse becomes weak and irregular, the skin cool and covered with cold sweat, and the countenance livid, the mucous membranes cyanotic, and the abdomen distended by extreme meteorism. With these are associated muscular cramps, at first localized, but gradually becoming general; all reflex action is lost, and, last of all, death occurs with violent convulsions.

The descriptions of different authors differ from one another only in very slight and unimportant particulars. Thus some describe furious delirium, whilst others mention trismus and tetanus as complications. And although the clinical picture of acute poisoning by sulphuretted hydrogen has not yet been drawn very accurately—for instance, we have no precise observations as to pulse, temperature, excreta, etc.—yet we are able, from the materials before us, to refer all the symptoms observed, with great probability, to the disorders of respiration—whether the altered properties of the blood, or a direct action on the nerves brings about this disorder, seems immaterial. If recovery takes place, as with timely and appropriate treatment it often will, the after consequences and sequelæ are, as a rule, very slight. The encephalitis which some authors have noted as a sequela can scarcely be considered to arise in direct consequence of the poisoning by sulphuretted hydrogen. And the terminal convulsions, which have been attributed to direct irritation of the spinal cord, we, on the contrary, unhesitatingly consider as spasmodic movements due to suffocation.

Unmistakable cases of chronic poisoning by sulphuretted hydrogen, apart from those instances of "self-poisoning" previously mentioned, are very rarely recorded, and the accounts of them are not very accurate. At the beginning the symptoms usually consist in subacute gastritis, with frequent hiccup and vomiting, constipation, colic, jaundice, etc., and a number of general nervous symptoms, such as lassitude, headache, vertigo, etc. V. Hasselt (loc. cit.) thinks that the *tout ensemble* of the symptoms of poisoning in these cases is very similar to, and may be mistaken for, subacute forms of typhus or rather typhoid fever.

Th. Clemens (loc. cit.) saw a number of workpeople in a chemical factory fall ill, one after the other, in the space of a few days, with general weakness of the extremities, want of appetite, oppression at the stomach, and vomiting—from, as it afterwards turned out, the use of well-water impregnated with sulphuretted hydrogen (Hydrothionsäure). The pulse was remarkably slow and easily compressible. All the secretions were sluggish, and the dry, cool skin had lost its usual turgescence or tonicity. In from four to ten days after the first stomach symptoms, the skin of the face, head, and hands, less often of the chest and extremities, was attacked with painless swellings, not actively inflamed, but soon developing into pustules and boils, with a great tendency to scabbing. Each boil was about the size of a hazel-nut. As soon as the skin became affected, the general symptoms ameliorated, only a peculiar blunting of the sense of taste remaining for a long while. Sulphuretted hydrogen was clearly proved to be the cause, and the fulfilment of the causal indication (leaving off the use of the water) led to rapid recovery in some cases where other means had long been tried in vain.

In the cases frequently mentioned before, of "self-poisoning," the beginning of the poisonous action was either indicated by a change of the previous symptoms (Emminghaus), by the general health suddenly declining, the occurrence of a bluish coloration of the face, the finding of the poison in the excreta, and, as the malady gained power, by death ensuing, or the symptoms mentioned above as indicating chronic poisoning were present in a more or less marked degree (Betz, Senator).

The *post-mortem appearances* in men dying from poisoning by sulphuretted hydrogen agree very closely with those found in *suffocation*. Indeed, except the not invariably present smell of hydrogen sulphide, which may also occur as a putrefactive phenomenon in other corpses, there is a total absence of any characteristic or pathognomonic symptom of hydrothion gas poisoning. Some authors, and indeed Casper (loc. cit.) in particular, have insisted on the inky blackness of the blood, and on the simultaneous discovery by the microscope of broken-up red blood-discs. But very little importance can be attributed to the often mentioned venous hyperæmia of the organs of the central nervous system, or to the various colors of the mucous membrane of the intestinal tract, which have been specially mentioned by Fabius and Devergie.[1]

It is almost self-evident that the very first point in the treat-

[1] See *Husemann*, loc. cit.

ment of poisoning by sulphuretted hydrogen must be to get the patient out of the injurious atmosphere. But, as has been said above, the fulfilment of this indication very often causes fresh victims ; and, therefore, very great caution is necessary in their deliverance. A number of prophylactic regulations to guard against the poisonous gas have been proposed by one and another. Most of these belong rather to the domain of legal sanitation. But if one be desirous to remove an unfortunate fellow out of a very dense atmosphere of sulphuretted hydrogen (as, for example, from a sewer, or the pit of a closet), since any previous disinfection of the place is generally impossible, use may be made of a sponge dipped in a solution of chlorinated lime, and bound in front of the mouth—although we cannot guarantee the absolute safety of even this plan. In very limited spaces, the hydrogen sulphide may be set on fire. But the safest and most serviceable method in all cases would be for those who enter the poisonous atmosphere to be provided with a mask for the face, like that used by divers, with a tube attached, communicating with the outer air. Such masks must of course be considered as part of the indispensable outfit for scavengers.[1] Most toxicologists (Hasselt, Husemann, and others) recommend beginning further treatment with an *emetic*, to get rid of anything swallowed. Tartar emetic must not be used, as this would be decomposed by the poisonous gas. And Clemens states that he found antimony useless in these cases. Instead, however, of using ipecacuanha, as Hasselt recommends, it would perhaps, in the present day, be better to use apomorphia, subcutaneously injected. *Artificial respiration*, as soon as ever any failure of natural breathing occurs, seems far more desirable than emetics. Many authors recommend the *inhalation* of chlorinated soda, chlorine water, solution of chlorinated lime, and, indeed, of chlorine itself, in order to render harmless any hydrogen sulphide present in the blood. But, as Husemann justly says, such measures are not quite free from danger, for chlorine itself must be considered as

[1] [Where no apparatus is at hand, holding the breath and attaching the body to a cord held by those in safety may sometimes succeed. And a bit of flexible tubing might possibly be obtained at short notice, in large towns, and inserted in the nostrils or mouth, so as to keep up connection with pure air.—TRANS.]

a poisonous gas. Besides, the gas appears to be eliminated in a natural (physiological) way with quite sufficient rapidity, provided only that the respiratory process can be kept efficiently going.

CHAPTER X.

POISONING BY PRUSSIC ACID AND ALLIED SUBSTANCES (VENENA CYANICA).

The practically important poisons of this group all act in proportion to the prussic (hydrocyanic) acid they contain or represent; they are partly products of the vegetable kingdom, and partly artificial chemical products. Pure cyanogen gas itself possesses intensely poisonous properties, which seem analogous to those of prussic acid. We need not, however, devote any space to the consideration of this gas, as it is not of any importance or significance in practical toxicology.

In the vegetable kingdom, prussic acid is generated through the action of an albuminous ferment, *emulsine* (Synaptase), on the nitrogenous glucoside, *amygdalin.* The action of these two substances on one another generates prussic acid, sugar, and oil of bitter almonds. A poisonous action has very often, but erroneously, been attributed to the latter essential oil, but recent investigations have shown that when chemically pure, and perfectly free from the prussic acid which is so firmly combined with it in general, it possesses no action beside that common to other essential (ethereal) oils. The oil of bitter almonds met with in commerce is, however, as a rule, strongly impregnated with prussic acid, and therefore intensely poisonous. The reaction of emulsine on amygdalin, so deeply interesting from a chemical as well as from a toxicological point of view, only takes place in the presence of water, and does not happen if the emulsion has been heated to the temperature of boiling water (100° C.). The ferments found in the bodies of animals, and particularly the gastric juice, appear to prevent this action of emulsine. Emulsine and amygdalin themselves do not appear to possess any poison-

ous properties. That other substances originating in the bodies of animals can decompose amygdalin and form prussic acid appears probable, as regards rabbits, from the experiments of Koelliker and Mueller.[1] The substances generating prussic acid are found more especially in bitter almonds, the fruits of *amygdalus communis*, var. *amara*, and in the cherry-laurel (*prunus lauro-cerasus*); also in the stones and kernels of peaches and plums, and several other members of the amygdalaceæ and pomaceæ.[2]

Amongst the chemicals containing prussic acid, the only generally important ones are prussic acid itself (hydrocyanic acid, HCy), and its alkaline salt, the potassium cyanide, (KCy). Some few cases are recorded of poisoning by ammonium, zinc, and mercury cyanides. As prussic acid is to be regarded as the essentially poisonous principle in all these, we propose to discuss the action of this acid, for all that is said about this may, with very slight individual modifications, be extended to all the other combinations of cyanogen.

The most important toxicological character common to all the cyanogen compounds is the characteristic smell of bitter almonds which they either exhibit, from the very first, or develop after solution or decomposition in the juices of the animal body. As regards prussic acid, it is to be noted that it is rare to meet with cases of poisoning from the anhydrous or concentrated acid. Most of the poisoning cases occur with various strengths of dilute acid. The strength of the various officinal preparations of prussic acid varies in different countries from 1 to 15 per cent. of anhydrous acid.[3]

Prussic acid is very volatile, and is soluble in water and alco-

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[1] Verhandlung der physikal.-med. Gesellschaft zu Würzburg. 1856.

[2] See *Husemann*, Pflanzenstoffe, p. 684, etc.

[3] According to *Husemann* (Toxikologie, p. 711), the officinal hydrocyanic acids contain as follows: in the Prussian, Bavarian, Austrian, American (U. S.), London, Dutch, Hanoverian, and most other pharmacopœias, 2 per cent. real acid. The Edinburgh pharmacopœia directs 3.2 per cent; the Dublin, 1.6 to 2.82 per cent; the Würtemberg, 3 per cent., and the French, 15 per cent. A strictly accurate and certain determination of the strength in real acid of any solution is, however, as *Husemann* insists, a problem which offers considerable difficulties in its solution.

hol under almost all conditions. Potassium cyanide is a very hygroscopic crystalline compound, easily soluble in water, and alkaline in its reaction. For the other physical and chemical properties of the *venena cyanica* we refer the reader to handbooks of chemistry and pharmacy.

The absorption of hydrocyanic acid into the animal body takes place very easily, and in several different ways, on account of the volatility of this compound and its easy solubility in watery fluids. The rapid action of its vapor, when inhaled, is well known; and its absorption into the blood is not much less rapid when applied to the mucous membrane of the digestive tract, to the subcutaneous connective tissue, or to raw surfaces, such as wounds. Its more rapid action, when ingested by the organs of respiration, is easily explicable when we consider that the large absorbing surface of the lungs enables a great quantity of this easily diffusible poison to reach the mass of the blood. Preyer's[1] opinion, that in this way of application there is an immediate stimulation or irritation of the peripheral branches of the vagus in the lungs, appears to us not justified by facts. Apart from the fact that the poison acts still more rapidly when injected into a vein, Preyer's view is not supported by the circumstance that even when the vagus is divided the ingestion of prussic acid gives rise to most violent symptoms of poisoning. To this we must add that the most recent researches—as will presently be further explained—leave it doubtful if the peripheral branches of the vagus play any particular part in poisoning by prussic acid.[2]

We do not consider that it has been proved that prussic acid can be absorbed by the skin, in the absence of any injury to that tissue, in quantities sufficient to poison. In regard to this we are at one with Preyer, who doubts Kuehne's assertion that gaseous hydrocyanic acid can penetrate the uninjured skin. For, apart from the probability of slight abrasions of the epithelial layer of the skin being overlooked, it is quite possible, in these cases, for the vapor of the acid applied to the skin to come in contact with the air-passages, and thus to get absorbed by the lungs. We do

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[1] Die Blausäure, etc. Bonn. 1868–1870.

[2] See Archiv f. exp. Pathol. und Pharmakologie. Bd. II.

not absolutely deny the possibility of absorption by the external integuments; for this poison is clearly not an indifferent agent as regards the skin, as is clearly proved by its local effects (in lotions, etc.), which are testified to by many observers. For if the feelings of insects crawling (Ameisenkriechen) and numbness, which follow the soaking the finger-tips in solutions of prussic acid, are considered only as affections of the local terminations of the sensory nerves, yet still, in any case, the poison must have penetrated the epidermis. And once admit this, there is then no special obstacle to the further absorption of the poison in this way. But the passage of large quantities of the poison into the blood in this way seems to be hindered by the diffusion of the bulk of the poison into the surrounding air. But a few experiments, made with the necessary precautions, ought to be capable of easily settling this point. Preyer, and also Coullon and Callies,[1] at an earlier date, did not observe any symptoms of poisoning follow the application of dilute prussic acid to the shaved skin in dogs and rabbits. But absorption through every possible mucous membrane, through serous membranes, and through the subcutaneous connective tissue, has been established beyond doubt by numerous experiments and observations, both old and new.

But can poisoning occur without the blood being implicated? Can this poison act without having passed into the blood? The results of experiments in which this poison has been applied to nerve-trunks laid bare, and to the surface of the nervous centres, would lead us to answer this question in the negative. The elimination of prussic acid from the animal[2] organism has not yet been studied with much accuracy, and the opinion that it takes place chiefly by the lungs and skin is based on the rather uncertain detection of the smell of prussic acid in the expired air, and in the perspiration of those poisoned.

As regards the behavior of the absorbed prussic acid in the organism, almost the only certain fact appears to be that, as a

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[1] See *Preyer*, loc. cit. pp. 41, 43.

[2] Consult *Preyer* for experiments by *Emmert*, *Wedemeyer*, *Schubarth*, *Gottwald*, *Kuerschner*, and *Krimer*.

rule, it is always possible to demonstrate a certain amount of undecomposed or free hydrocyanic acid in the blood. The discovery made by Preyer and Hoppe-Seyler,[1] that the blood-pigment forms a crystalline compound with prussic acid, appears to us to help our explanation of the symptoms in cases of poisoning by prussic acid, very much in the same way as the analogous discovery of carbonic oxide hæmoglobin does, in poisoning by carbonic oxide. But in this case the combination of the poison with the hæmoglobin has been demonstrated in the blood of living animals thus poisoned, whilst, as regards prussic acid poisoning, this is not yet the case. Schoenbein's experiments[2] have shown that hydrocyanic acid changes the vital properties of the red blood-discs, and robs them of their power of liberating oxygen from the peroxide of hydrogen.

The external phenomena due to the action of prussic acid are especially centred, in all warm-blooded animals, in disturbances of the respiratory movements; these are either more or less quickly abolished, or are excessively retarded. As a rule, the typical poisoning case commences with ten or twelve unusually hurried respirations, which are immediately succeeded by an attack of tetanic convulsions, during which the diaphragm remains contracted and immovable. Should the animal not die, as it generally does in this attack, then all the muscles become relaxed, and deep respirations succeed with very short *in*spirations, strikingly long expirations, and unusually long intervals between the individual breaths. If the animal recovers, these respiratory pauses gradually give way to more natural breathing; but if it does not recover, death ends the scene in less than an hour, without any fresh convulsive attack. After the first convulsive seizure, all reflex irritability and sensation are totally lost; but both return should the breathing again become normal.

A number of observations have been made in order to try to explain the disordered respiration. Thus, Gaehtgens[3] has dis-

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[1] Med. chem. Untersuchungen und Virchow's Archiv. Bd. 38. 1867. See also *Preyer*, Blutkrystalle and loc. cit.

[2] Zeitschrift für Biologie. Bd. III. p. 140.

[3] *Hoppe-Seyler*, Med.-chem. Untersuchungen. p. 346.

covered that the chemistry of respiration undergoes a change. The quantity of carbonic acid in the expired air is remarkably lessened during the poisoning, as compared with healthy animals, whilst the quantity of oxygen in it exceeds that of normal expired air—a result diametrically opposite to the rule of ordinary suffocation, and one not easily explicable by the mere admission of a simple disturbance of the mechanism of respiration. Gaehtgens' results led him to suspect that animals poisoned with prussic acid form less carbonic acid than usual, and take in less oxygen than the normal amount, so that, during the acme of the poisoning, the processes of oxygenation in the system are almost suspended. The physiological experiments of Preyer on the disorders of respiration in poisoning by prussic acid do not elucidate the question much, since they have not been confirmed by other investigators. Preyer insists on the action of the poison on the peripheral pulmonary branches of the vagus, and ascribes the fatal result to the irritation of these organs. He considers that his experiments justify the view that otherwise certainly fatal doses will not kill animals in whom the vagus has been divided, and indeed that such animals no longer die suffocated, but only from the paralyzing action of the poison on the heart. In an analogous way, Preyer holds that atropine, which paralyzes the vagus, preserves an animal from being suffocated by prussic acid. The author has lately repeated Preyer's experiments in conjunction with Knie,[1] but has not succeeded in obtaining the same results. On the contrary, he finds that section of the vagus nerves and atropine do not in any way modify the action of prussic acid. On the other hand, he was able to show that, at the acme of prussic acid poisoning, irritation of the central vagus fibres had no effect on the breathing, and did not stimulate the relaxed diaphragm to any contraction. And his results contradict Preyer's view, that respiration in prussic acid poisoning exhibits a spasmodic character as regards the *in*spirations, for, except in the first convulsive seizure, he never saw inspiratory tetanus as a result of prussic acid poisoning, but always found, in the pauses between the breathing,

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[1] Archiv f. exp. Path. und Pharm. II. 1874.

that the diaphragm was in the position of expiration, *i. e.*, at rest.

Next to the action on respiration, most attention has been devoted to the action of the heart in poisoning by prussic acid. In cold-blooded animals (frogs) this poison causes a very considerable decrease in the number of the apex-beats, and sometimes even at the commencement a diastolic arrest or stand-still, which subsequently yields to irregular and weak contractions. Preyer attributes very great importance to the cardiac vagus in prussic acid poisoning, and when the doses are not too large, attributes the whole of the symptoms to the changes in the innervation of the vagus—that is, to a temporary irritation or paresis of the inhibitory vagus. The absolute stoppage of the heart by very large doses is attributed to a direct paresis of the automatic nerve-centres of the heart itself (due to deficient oxygenation of the blood). The author's experiments in this direction, however, yielded results very different from those of Preyer. He could not establish in the least degree, that the inhibitory vagus is at all implicated by the action of prussic acid on the organs of circulation. The stoppage of the heart always *followed* the cessation of respiration, and never preceded it, no matter whether section of the vagi had been performed or not. It was never possible in cats to observe any stoppage of the heart by direct irritation of the vagus in an early stage of the poisoning. Indeed, we were led to the conclusion, that it is by no means easy to kill the heart by doses of prussic acid. For if death by asphyxia were hindered by artificial respiration, even when enormous doses of the acid were given, the heart beat regularly, though rather slowly, until the animals finally recovered from the poisoning. The blood-pressure and the pulse-frequency, after being slightly increased for a few seconds by prussic acid, became considerably lessened.*

Experiments on cold-blooded creatures (frogs) and other animals, for the most part, agree with one another, and lead to the conclusion, that for all classes of animals this is one of the most deadly poisons. We need not here give references to these in detail. It may be propounded as a general rule, that the more active the tissue-changes in any animal are, the more sensitive

will it be to the action of the poison. For example, birds succumb most quickly and completely, whilst cold-blooded animals, like frogs, whose respiratory needs are slight, succumb rather slowly to the action of the poison, which in them seems almost limited to a gradual annihilation of the power of voluntary movements, whilst fishes are still more slowly affected by prussic acid.[1]

It will be seen, however, that numerous as are the experiments and observations on the poisonous action of prussic acid, and varied and many-sided as are the points of view in which we may regard them, yet when we attempt to draw any conclusions as to the precise manner in which this poison acts, we are met by precisely the same kind of difficulties which prevented our coming to a definite conclusion in the case of poisoning by carbonic oxide, sulphuretted hydrogen, and other poisons. This is just that interesting group of poisons which appears to us to offer for the first time, in the dark domain of toxicology, points of analogy and resemblance between purely physiological and physiologico-chemical effects. But this only makes it more dangerous to draw premature conclusions, or accept crude theories. But until something more is known we are justified, in the present state of our knowledge, in concluding :—

That prussic acid has an extremely prejudicial action on the respiratory functions of warm-blooded animals.

And that paresis of the respiratory centres appears to be the real cause of death in this mode of poisoning under all sorts of circumstances.

The action of prussic acid on the heart and circulatory organs originates partly in the respiratory disturbances and partly in a directly paralyzing effect of the poison on the vaso-motor nerves; in animals free from injury the latter is never a cause of death. We consider the convulsions of prussic acid poisoning as the expression of a transient but energetic irritation of the central apparatus of the brain and spinal cord, and do not think they can be identified with the ordinary convulsions met with in simple suffocation. What rôle the above-mentioned changes in the

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[1] See *Preyer* (loc. cit. II. p. 45 et seq.) for details on this point.

chemistry of the blood and of the tissues play in the state of things brought about by prussic acid poisoning is at present absolutely dark and obscure, and, until something further is discovered, the opinion of a directly poisonous action of hydrocyanic acid on the functions of the central nervous system seems to be the only possible explanation. Suicidal attempts and medicinal poisonings by misadventure furnish the greater number of cases of poisoning by prussic acid; but with these are associated also a few cases of purely accidental poisoning, particularly in consequence of the modern technical applications of potassium cyanide (in gilding, silvering, etc.) and the use of vegetable substances containing prussic acid as articles of diet. Unfortunately, there is a deficiency of any very precise determination of facts in the recorded literature. Tardieu and Roussin very properly remark that it is quite possible that a large number of cases of poisoning by prussic acid are never discovered, and that it would be very erroneous to attempt to draw any conclusions as to the frequency of these cases from the number of those recorded. It is therefore almost a matter of astonishment that the number of known suicides by means of venena cyanica is so small. Without, therefore, attaching any undue importance to mere numbers, we record some figures taken from a collection of the more carefully recorded cases of poisoning by prussic acid from the literature of the last twenty years. Of 35 cases 13 were medicinal poisonings, 11 were suicidal, 6 were economic or accidental poisonings in trades, etc., and 5 were designated as murders. Only 2 recovered, whilst 33 ended fatally; 30 of these were in males, and 5 in females. Of the medicinal poisonings some were due to the prescriber's mistake, and some to the fault of the compounder in mistaking the dose. In the celebrated case at the Bicêtre in Paris, recorded by Orfila,[1] seven men fell victims to the stupidity of an attendant, or male nurse, who gave them an overdose of a prussic acid mixture. Accidental poisonings sometimes happen in surgeries and chemists' shops; thus the breaking of a flask filled with strong prussic acid proved fatal to an apothecary's apprentice, who succumbed to the rapidly dif-

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[1] Annal. d'hygiène publ. 2. sér. XXX. 1868.

fusing fumes of the poison. Similar cases occur in chemical laboratories; thus the death of the celebrated chemist Scheele is known to have been caused in this way. How very little injurious the contact of solutions of potassium cyanide with the uninjured skin really is, the daily experience of photographers constantly shows.

Tardieu and Roussin[1] point out that the uses of potassium cyanide in gilding and silvering furnish fresh opportunities for cases of poisoning. Chanet attributes these for the most part to the vapors of prussic acid which thus become diffused through the work-rooms. Taylor[2] also has convinced himself of the presence of vapors of prussic acid in gilding by the galvanic process. The use of Berlin blue in dye-works may give rise to poisoning by prussic acid. But all the technical cases of poisoning by prussic acid are less productive in the way of poisoning than suicide.

Amongst the poisons of vegetable origin, bitter-almond oil is the most common. It is used in the fabrication of liqueurs (Maraschino) and confectionery, and also, though less often, in perfumery. Bitter almonds, in substance like the kernels of plums and cherries, may give rise to poisoning. The officinal preparations of this group are bitter almond oil and water (U. S. Ph.), and cherry-laurel water (Br. Ph.). Except the oil of bitter almonds, none of these contain any great amount of prussic acid. Yet experience shows that they sometimes prove very deadly, particularly to children.

The determination of the fatal, or even of the poisonous dose, is beset with more difficulties, and is less certain than in the case of almost any other poison. We have to contend not only with the great variety in the strengths of the officinal preparations, but also with the great volatility of the poison and other difficulties. It has been attempted to determine the fatal dose in various classes of animals. For human beings, however, there are no very reliable figures. According to Husemann,[3] we may consider one grain (0.061 gramme) of anhydrous prussic acid equal

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[1] Gazette des Hôpitaux. 1847. [2] Loc. cit. III. p. 83.

[3] Loc. cit. p. 711.

to two and one-half grains (0.152 gramme) of potassium cyanide, as the smallest fatal dose for grown-up people—numbers which may at least stand as a sort of general representation of the relative poisonousness of the different forms of prussic acid. That smaller quantities may have caused death, or that larger doses may sometimes have been tolerated, appears to us to be attributable to idiosyncrasies or individual peculiarities, which cannot well be calculated, and to the difficulties in the way of determining accurately a general formula applicable to all cases.

As regards the other phenomena of cases of poisoning by this acid, we may say that it is notable for the rapidity with which it kills, and although the accounts given of its almost lightning-like rapidity of action must not always be taken quite literally, yet after the ingestion of a large dose of the poison it commonly requires only a very few minutes to terminate life. The division into stages, adopted by most toxicologists (such as a stage of asthma, one of convulsions, one of asphyxia, one of coma, etc.), appears to us unnecessary, and rather likely to lead to false views. The duration of the whole drama is in general so brief that, however allowable in theory, any division into stages cannot be practically carried out in most cases. But experiments on animals and observations in human beings appear to us to show that even in theory any division into stages is untenable. The whole of the symptoms, from beginning to end, are the result of disordered respiratory functions, and the shades of difference between one moment and another are unfortunately so gradual and so slightly diverse that they usually glide imperceptibly one into the other without any marked separation between them, and the more rapidly the larger the dose of the poison ingested. On the other hand, it does appear desirable to make a distinction between the very acute cases and the less severe forms of poisoning, for this is a practical distinction; to the first category belong the cases described as occurring with lightning-like rapidity, and which terminate fatally in a few minutes without the sufferers being able to give any account of themselves; whilst those cases which terminate more slowly, either in death or recovery, belong to the second class.

In the first cases scarcely a minute elapses after the first tak-

ing of the poison before the symptoms of poisoning commence with sudden loss of consciousness—and in some cases the poisoned person falls to the ground with a loud cry or shriek. It is not at all unusual for a short attack of general convulsions to supervene at this moment. This is immediately succeeded by a condition which is essentially characterized by the peculiar kind of respiration. Each breath follows the other just as has been described in experiments on animals, tediously and spasmodically—the inspiration short, the expiration greatly protracted, but immediately following the short inspiration; between the expiration and the next inspiration succeeds a pause, which becomes longer every time, in which the patient, as all observers agree, lies as if dead; and, in fact, death actually occurs in one of these pauses, and simply consists in the absence of any fresh inspiration.[1] The expired air in such cases is often said to have the smell of prussic acid.

The eyeballs of those poisoned are strongly prominent, the pupils, as a rule, moderately dilated; and, like the other forms of asphyxia, prussic acid poisoning is for the most part accompanied with a good deal of salivation, which is probably the reason why foam covers the mouth. The jaws are usually somewhat firmly pressed together, so that the freely secreted saliva, in the recumbent position of the body, is easily changed into foam by the spasmodic breathing. Whilst the general surface of the skin feels cool, and is covered with cold, clammy sweat, the visible mucous membranes generally show a slight cyanotic tinge. The face is here and there reddened and swollen, but towards the last it is generally pale and collapsed. In the facial muscles, as well as in the extremities, slight muscular spasms occur. The sensorium is perfectly in abeyance, and even reflex

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[1] This peculiar respiration is a further proof of the incorrectness of *Preyer's* view that prussic acid poisoning commences with tetanic inspirations. Many observers of cases of poisoning in the human subject expressly call attention to the spasmodic, long-drawn expirations. We must therefore decidedly protest against a correction which *Preyer* himself has made in the paper of another author (loc. cit., II., p. 103), in which he accompanies the expressly mentioned "spasmodic *ex*piration," with the words in parenthesis, "should have been written *in*spiration." It would certainly not be difficult in this way to harmonize the observations of others with one's own opinions.

movements are absent. The pupils do not react with light, and there is no response to irritation of the skin. The muscles are relaxed, and no trace of voluntary movement is present. The pulse, which at first is somewhat increased in frequency, becomes at a later period weak, rarely intermittent, and at the acme of the poisoning can generally no longer be felt. There are no observations of temperature in men, yet the heat of the body appears to be decidedly decreased. Urine and fæces are sometimes passed involuntarily at first, and at a later stage they are suspended.

In this form of poisoning death occurs within fifteen minutes after the swallowing of the poison.

In less violent cases there are sometimes some subjective symptoms or complaints. The poisoned person sometimes complains of the bitter, somewhat burning taste of the poison, and of a feeling of constriction in the throat. With these, in the course of one or two minutes, are associated gradually increasing vertigo, palpitation, confused consciousness, obscuration of the field of vision, pain and pressure in the head, precordial anxiety, and extreme weakness of the voluntary muscles. With these symptoms, which are usually accompanied with nausea, the poisoned person generally loses his senses, becomes devoid of sensation, and is attacked with severe general convulsions, usually epileptiform. Yet even in this case, the convulsions usually give place to general paralysis of muscles, and then we generally get various modifications of the symptoms of asphyxia which have been described before, and these in longer or shorter time (from some hours to two days) end in death, or gradually, and without any special complications or sequelæ, terminate in recovery. Dr. Taylor justly remarks that in those cases which recover, recovery is often preceded by vomiting. Both *ructus* and *flatus* may sometimes exhibit the smell of prussic acid.

The questions, whether there is such a thing as chronic poisoning by prussic acid? whether this poison is cumulative? and whether the system can be at all accustomed to it? are questions which cannot be certainly answered on the basis of our present experience. The slight symptoms which follow the reception of small quantities of the poison, particularly in a gaseous form,

consist, as a rule, in some headache and stupidity, slight oppression, threatened vertigo, lassitude, and vomiting. The susceptibility of different persons to the action of the poison varies considerably.

It is quite certain that the vegetable preparations of prussic acid, and the chemicals, prussic acid and potassium cyanide, perfectly resemble each other in their effects. As regards the other, venena cyanica, our toxicological experience is very slight. Ammonium and zinc cyanides appear to produce the same effects, at least qualitatively, as the substances described; whilst, as regards mercuric cyanide, it seems doubtful how far its effects are due to mercury, and how far to cyanogen.

The *post-mortem appearances* in poisoning by prussic acid are, from a pathological point of view, purely negative; only the chemical investigation of the blood and of the viscera may sometimes succeed in obtaining traces of the poison, and in some cases the body has a remarkable odor of prussic acid all over it. No alterations of texture can be discovered, either macroscopic or microscopic; and neither the color, properties, nor distribution of the blood in the body can furnish us with any certain signs of death from prussic acid or the poisonous cyanides.

Although Preyer believes that in atropine he has discovered a perfect antidote to prussic acid poisoning, yet newer experiments have shown us that we cannot recommend it as such. We are rather inclined, in these cases, to rely on the same mechanical aids as are applicable in other forms of asphyxia; for the other so-called antidotes, such as ammonia, etc., are at least of doubtful value. After fulfilment of the causal indication, that is, the removal of or from the poison, so far as practicable, we had better proceed at once to *artificial respiration*, and this should be aided by all the means at our command, until respiration be re-established in its integrity. Counter-irritants to the skin and mucous membranes may be applied, as in other cases where life is in danger. *The injection* of *ammonia into a vein* has lately been recommended warmly as a powerful stimulant in asphyxia, and favorable cases have been detailed as encouragements to this practice. We cannot cordially recommend this until further experiments on animals have been made. But *depletory transfu-*

sion seems likely to be of use, although it is in itself a measure so severe that it seems scarcely right to try it merely as an experiment in cases of real severity.

SECOND DIVISION.

Poisoning by other Poisonous Compounds of Carbon.

CHAPTER I.

POISONING BY BENZIN (BENZOL, C_6H_6).

Benzin is obtained in large quantities by distillation from coal tar naphtha, which contains from three to four per cent. of it. At ordinary temperatures it is a colorless, highly refractive liquid, which floats on water, is very volatile, but does not boil below 80°–85° C.=176° to 185° F.

The observation that benzin is a powerful insect poison, and destroys other low forms of animal life, has led to its being employed as a parasiticide in both men and animals. Indeed, Mosler[1] has especially recommended it as a powerful remedy for intestinal trichinæ.

As the long-continued inhalation of the vapor of benzin causes symptoms of stupefaction in human beings, Simpson and Snow made experiments to see if it could be used as an anæsthetic, but they came to the conclusion that the narcosis from benzin was not only very difficult to obtain, but was associated with unpleasant symptoms—noises in the head, muscular tremors, and such like. Mosler and others have established the fact that benzin may be taken internally in pretty large doses (two drachms a day) without any injurious effects. In spite of

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[1] Berlin. klin. Wochenschrift. 1864. No. 32.

the great use made of benzin in the arts and manufactures there has, till quite lately, been only one recorded case of poisoning by benzin—that of Perrin [1]—which resulted from swallowing a large quantity of benzin. The symptoms were those of simple narcosis, terminating in deep sleep and final recovery. According to a verbal communication of Professor F. A. Hoffmann, there was, some years ago, a case in the Charité Hospital, at Berlin, of considerable interest, because it commenced with the symptoms of corrosive poisoning. The patient was said to have taken a large quantity (?) of benzin with suicidal intent, and died after some days of purulent pleurisy, which originated in a perforation of the œsophagus. Unfortunately, no further details of the case could be obtained. [Sir W. Gull's case ended in recovery.]

CHAPTER II.

POISONING BY NITRO-BENZIN.

Nitro-benzin, or nitro-benzol ($C_6H_5NO_2$), is formed out of benzin, or benzol, when this is dissolved in concentrated nitric acid, and the solution decomposed with water. Like anilin—to procure which for commercial purposes it is employed—it is a poison, and from a toxicological point of view is deserving of even more attention than this, because of its extensive use in factories and in the arts, which gives rise to such numerous opportunities for its injurious action on human beings. At the exhibition of 1851, in Paris, it was offered for sale, under the name of "*Essence of Mirbane*," as *harmless* perfumery. It is a bright yellow, oily sort of fluid, heavier than water, of 1.209 specific gravity, and has a very penetrating odor of bitter almonds. The taste is unpleasantly bitter, and it causes a sort of scraping or sore feeling in the throat. It does not mix with water, but easily mixes with alcoholic and oily fluids. To these properties it owes its uses in the adulteration of liquors, pomades, hair-oils, etc. The taste is easily recognizable in very small quantities, and is far

[1] L'Union méd. 1861. No. 6.

more lasting and intense than that of bitter almond oil (essential oil of almonds), for which it has been used as a surrogate or substitute, and was originally intended as such. The long persistence of the smell of this substance in all bodies with which it comes in contact may be explained by its very slight volatility and its high boiling point (220° C. =428° F.).

Like anilin, nitro-benzin may pass into the circulation in animals in the form of vapor, and produce its effects. Its absorption by mucous membranes, and by the subcutaneous connective tissue, takes place very slowly, and according to Guttmann[1] not more rapidly by the latter than when applied by the mouth. However, there are no very precise observations on the absorption of nitro-benzin. Bergmann[2] has demonstrated the extreme slowness with which it is absorbed in a liquid form. He found, after administration of three drops to a dog, that drops of this substance were present in the stomach three days after, though the dog was poisoned by it. Ollivier and Bergeron assert that they have found drops of this poison in the blood, and in the glandular organs of the animals which have been poisoned by it.[3] But as this has not been confirmed by any other observers we must receive it with great caution. The intense action of the vapors of nitro-benzin would rather lead us to consider that no liquid nitro-benzin gets into the blood, but that even in the stomach the poisonous action occurs from the vapors or fumes of the poison getting into the blood. Nothing certain is yet known as to the manner in which it is eliminated. The assertion of Dr. Letheby[4] that nitro-benzin is converted into anilin in the blood, acts as anilin, and is excreted in the urine, has not been confirmed by others, though many authors have directed especial attention to this point. We must except, however, Ollivier and Bergeron (loc. cit.), who state that they found anilin and picric acid also in all the viscera. This hypothesis of conversion into anilin must therefore remain a moot-point for the present.

In its action as a poison, however, nitro-benzin behaves ex-

[1] Arch. f. Anat. u. Physiologie. 1866.

[2] Prager Vierteljahrschrift. 1865. IV.

[3] *Brown-Séquard*, Journal de physiol. 1863. No. XXIII.

[4] Med. Chir. Review. 1863.

actly like anilin, as a nerve-poison, whose sphere of operations is the organs of the central nervous system. Guttmann has shown that the excitability of the peripheral nerves and of the striated muscles is left intact by nitro-benzin. A single drop on bibulous paper, placed under a bell-glass and allowed to evaporate, will, in three or four hours, produce paralysis and death in frogs. The mode of death is always that of simple general paralysis without convulsions or action on the heart.

In mammals, who perish by asphyxia, it is common to observe convulsions of some of the muscles—as, for example, of the masseters and muscles of the fingers and toes—as well as general tonic and clonic convulsions, just as in human beings. What department of the nervous system is thus implicated neither experiments nor clinical observations have yet enabled us accurately to determine. It is extremely interesting to note—though as yet inexplicable—that, both in poisoning cases in men and in experiments on animals, the symptoms of poisoning are very often delayed, or in abeyance, for a period which varies from several hours to a day or more, after the taking of the poison [and even longer in some of Dr. Letheby's cases.—TRANS.]. The slow absorption of the poison affords the most reasonable explanation.

As regards the etiology of nitro-benzin poisoning, the most important source has been indicated above. The workers in anilin dyes, the manufacturers of these, are of course constantly exposed to danger from the handling of, and constant vicinity to, this poison. Several accidents have happened by the careless sucking of syphons, in decanting nitro-benzin, and by the breaking of large carboys, etc., etc.

The adulteration of articles of diet and beverages with the poison is a second source of danger which gives rise to cases of poisoning. Besides its use in liqueurs, essence of mirbane has been added to sweetmeats for the sake of its odor. Streeter[1] gives a case in which a child was poisoned by sago, to which nitro-benzin had been added. In another case two male servants were poisoned by nibbling at a pomade made with nitro-benzin.

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[1] Medical Times. 1854.

Then there is the possibility of the nitro-benzin itself being mistaken for a beverage, especially a liqueur, on account of the smell. In this way, in the late Franco-German war, according to Helbig,[1] eighteen soldiers were poisoned, who had found in a villa a flask containing a fluid which they mistook for a liqueur, but which the surgeon discovered to be nitro-benzin. It killed three of them.

Up to the present date forty-two cases of poisoning by nitro-benzin have been placed on record; five were females and thirty-three males; fourteen, or one-third of all the cases, ended fatally. Exact details are wanting in four of these. Most of the cases (31) were accidental; four took place through handling the poison in factories where it was employed; and three were attempts at suicide, in one of which nitro-benzin was put into the suicide's hands instead of the essential oil of bitter almonds which he intended to use. The mortality will seem yet more serious if we deduct the instance, recorded by Helbig, where several were poisoned at the same time, for then eleven out of twenty-one cases, or more than half, ended fatally.

As regards the quantity of the poison taken in the individual cases we have very little precise information, and it is thus not possible to fix on a fatal dose, notwithstanding the number of cases on record. It is, however, quite certain, from a few of the cases, that very small quantities of the poison may cause death. Letheby (loc. cit.) mentions eight or nine drops as the quantity in one case. Mueller (loc. cit.) speaks of a teaspoonful, whilst Treulich[2] names a thimbleful. In Bahrdt's[3] case about twenty drops, in that of Aé[4] two drachms, caused death. It must especially be insisted upon that even in a gaseous form this poison may cause death, and always acts very energetically, but in this case it is still less easy from the nature of the case to determine the fatal dose.

The symptoms of poisoning by nitro-benzin in human beings have a considerable resemblance to those of anilin poisoning,

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[1] Deutsche milit.-ärztl. Zeitung. 1873. II.

[2] Wiener med. Presse. 1870.

[3] Archiv f. phys. Heilkunde. 1871.

[4] *Husemann*, im Jahresbericht von Virchow und Hirsch. 1871. I.

and are, like those, almost exclusively of a nervous kind. The remarkably long latent period of the symptoms has been often insisted on, particularly by Letheby and Bahrdt. Indeed, in the average of all cases, the fact was, that in general, though not quite universally, the first symptoms of poisoning did not develop themselves before from half an hour to two hours. But although this is not universal, and several cases have ended fatally in the course of the first eighteen to twenty-four hours after the ingestion of the poison, yet we cannot deny that the latency of the poisonous action may be a point of some practical importance in special cases as a means of diagnosis.

General feelings of discomfort, weariness, nausea, and a rapidly increasing peculiar dull benumbing of the head, are generally the first complaints of those poisoned. Several observers, even in this stage, have been struck with the dirty, livid coloration of the skin, particularly in the face; at a later stage this reaches a high degree of cyanosis. Spontaneous vomiting sometimes occurs. With increasing feelings of anxiety, want of breath, incapacity for clear thinking, and more and more confusion of the sensorium, the true narcotic symptoms are now more or less quickly developed. These sometimes assume the character of irritant symptoms, sometimes they are more paralytic. It is very frequently mentioned in the accounts given of poisoning by nitro-benzin that there were severe general convulsions and contractions of particular muscular groups; in some few cases, indeed, trismus and tetanus have been noted.[1] At the height of the poisoning consciousness is generally quite lost, as well as sensation and reflex irritability.

The pupils are dilated, but, as a rule, they still act, though feebly. Some observers, as B. Kreuser, have noted contracted pupils. Bahrdt and Kreuser observed continual rotary spasms of the ocular muscles. The external integuments show characteristic colorations. The face has sometimes been described as bluish-gray, sometimes as ashy-colored; the lips as purplish-red, and the fingers as bluish-black.

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[1] Compare *Schenk* (loc. cit.), *Kreuser* (Würtbg. Corr.-Bl. 1867), *Ewald* (Berlin klin. Wochenschr. 1875. No. 1).

Pulse, respirations, and temperature present their usual characters in such conditions, and offer no special characteristics. Either a convulsive or a comatose stage precedes death by asphyxia.

As a rule, any localized symptoms of irritation are absent, except vomiting, pains in the abdomen, and a feeling of irritation, like scraping, in the throat, of which those who swallow the poison sometimes complain. Letheby and Schenk have noticed that the tongue is swollen, and of a whitish color. The vomited matters, as well as the breath, always smell strongly of the poison, and thus render the diagnosis easy to those who can distinguish the smell from that of prussic acid, which is not difficult when once learned.

Ewald states that he has lately [1] discovered sugar in the urine of these cases. The cases which do not end fatally are generally protracted by considerable disturbance of the general health succeeding the poisoning. Want of appetite, muscular weakness, headache, noises in the ears, and a sense of oppression (Eingenommenheit) are the principal inconveniences met with. No permanent pathological changes occur.

The results of all the *post-mortem examinations* made as yet have been so far negative, inasmuch as no changes have ever been discovered in the organs of the body which could in themselves establish the fact of the poisoning. The only reliable fact, therefore, is the scarcely ever absent smell of the poison, which for a long time closely adheres to the whole body of the poisoned person, and especially pervades the internal organs. This durability of the smell of nitro-benzin serves as a characteristic, by which we may distinguish it from the somewhat similar, but more transient smell of prussic acid. As the residue of a moderate amount of irritation during life, we sometimes find catarrhal swelling and redness of the digestive tract, and occasionally, also, ecchymoses in the mucous membranes.

Having regard to the slowness with which nitro-benzin is absorbed, it will always be proper to *begin the treatment of a case of poisoning by nitro-benzin by endeavors to remove any of*

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[1] Med. Centralbl. 1874, u. loc. cit.

the poison which may remain in the stomach. Whether *emetics* or the *stomach-pump* should be used must depend upon the particular case. If this indication be fulfilled, the rest of the treatment must depend upon the symptoms. That particular attention should be paid to pulse and respiration is easily to be understood. If the respiration be much interfered with, the use of *artificial respiration* may be essential.

There is as yet no known rational antidotal treatment against nitro-benzin poisoning.

CHAPTER III.

POISONING BY ANILIN AND ANILIN DYES.

The substance called anilin (C_6H_7N), which may be called the mother-dye of all those beautiful coloring matters which play so important a part in modern industry, is an organic base, which unites with acids to form crystalline salts. It is obtained in large quantities from nitro-benzin, and in a chemically pure state is a colorless, oily sort of fluid, of peculiar smell, and of burning, bitter taste. Its reaction to test-paper is neutral; air and light gradually turn it yellow, and even at ordinary temperatures it gives off copious vapors, which can be recognized at once by their smell, which is characteristic. No one, nowadays, doubts the poisonous nature of anilin, both as regards the free base and its salts, since, on the one hand, practical medicine has had to do with many indubitable cases of anilin poisoning; and, on the other hand, toxicologists have proved its poisonous properties by numerous experiments on animals. As regards anilin dyes, however, the case is somewhat different. We cannot generalize as to their being poisonous or not, but each must be separately dealt with. It is not possible here to go into great detail on this point, but we may mention that the injuriousness of the colors is, as a rule, due to admixtures, which are sometimes substances used to oxidize the anilin (arsenic acid, for example), whilst sometimes it depends upon undecomposed anilin (the parent-dye) being present. We can only consider the latter

cause now. It is, to say the least, doubtful if any of the anilin colors are poisonous in and by themselves alone.

The innocuousness of the well-known anilin colors, known under the names of fuchsin, azalein, Magenta red, etc., etc.,[1] has been put beyond question by the investigations of Sonnenkalb[2] and Bergmann.[3] The cases of poisoning which have, notwithstanding, been due to the colors above named — as, for example, one observed by Bergmann himself—must be attributed to an admixture of undecomposed anilin.[4]

The same holds good as regards corallin or pæonin, a red color composed of rosolic acid, to which Tardieu[5] ascribed very poisonous properties. Its harmlessness in a chemically pure condition, Landrin[6] and Guyot[7] have demonstrated. The rosolic acid, which in itself is harmless, is often, as Eulenberg and Vohl and Guyot found, adulterated or not freed from carbolic acid. This explains the apparent contradiction between Tardieu's observations, and the local diseases which are observed to be caused by the use of articles of clothing colored with corallin. There are a good many of these cases, well authenticated, but we cannot consider them here at any length. For the most part, they consist of eczematous or papular skin-diseases, in consequence of the wearing of colored socks, or hosiery dyed with corallin, or the use of red flannel shirts. In some of the cases, this is due to the arsenic contained in the red colors. The poisonous symptoms produced by certain green aniline colors, since they were caused by the presence of arsenic, will also be considered in another part of this volume.

Free anilin may, by means of its volatility, get into the circulation, not only by way of the stomach, but also through the lungs; whether it can pass through the skin also has not been settled. Lailler's[8] two cases, in which after the external application of muriate of anilin in psoriasis, there were symptoms of anilin poisoning, do not, as we believe, prove that the uninjured skin can absorb free analin. Authors differ from one another as to the way in which it is eliminated from the animal system. Bergmann (loc. cit.) recovered it from the urine, which Schuch-

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[1] These are salts of a basic substance, called rosanilin, which is itself colorless, or only faintly reddish. This itself is not at all poisonous. It is formed by oxidation from anilin and toluidin.

[2] Anilin und Anilinfarben. Leipzig. 1864.

[3] Prager Vierteljahrschrift. 1865. IV.

[4] See *Eulenberg* and *Vohl*, Arch. d. Pharmak. 1870. September.

[5] Comptes rend. LXVIII. 1869.

[6] Ibid. LXVIII. p. 1536.

[7] Ibid. LXIX. p. 388.

[8] L'Union méd. 1873. No. 67.

hard[1] (loc. cit.) and Sonnenkalb (loc. cit.) failed to do; these assert that the poison is excreted by the lungs. As regards the further changes undergone by anilin in the blood, nothing definite is known. Bergmann alludes to Turnbull's[2] view, that anilin is oxidized in the body to violet coloring matters—founded on the cyanotic coloration of the skin noticed in cases of poisoning—without confirming it. Besides its general action on the blood, anilin in a free state has a slight local action on the parts to which it is applied, and this clearly finds its explanation in the behavior of the free base when present in solutions of albumen, which are coagulated by this poison. If large quantities come into contact with mucous membranes, it may prove the exciting cause of gastro-intestinal symptoms. Bergmann only attributes very slight local irritant effects to this poison; in animals who took it some time he only noticed catarrh of the gastric mucous membrane, and he never noticed any abscesses after repeated injections into the subcutaneous connective tissue. But the changes produced in the mass of the blood in consequence of this poison are far more serious. These have the general character of narcotic poisoning, and are limited to the functions of the central nervous system.

The experiments of Schuchhard, Bergmann, and Sonnenkalb leave no doubt on the point that, both in cold- and warm-blooded animals, this poison acts like other narcotics, by altering the functions of the brain and spinal cord. Muscular contractions and general convulsions, anæsthesia, and paralysis of motion, are the symptoms thus caused. The excitability of the peripheral motor nerves, as well as of the muscles, remains intact. The action of the heart is only disturbed in a secondary manner, that is, in consequence of the affection of the muscles concerned in respiration and the defective aeration of the blood, induced by their paralysis. Experiments on frogs show that anilin is not a poison to the heart. The question, whether anilin exerts any special or specific influence on the nervous centres for breathing movements, has not yet been solved by any experiments which have yet been made, although they have proved that

[1] Virch. Archiv. Bd. XX. [2] Lancet. 1861.

anilin death, in warm-blooded animals, happens through asphyxia.

The opinion of some French authors,[1] that the symptoms of anilin poisoning are caused by the changes produced in the blood by the poison, and not by direct action on the nervous centres, has not been confirmed; and the observations on which this hypothesis was founded, namely, the want of coagulation of the blood in anilin poisoning, and peculiar changes in the red blood-corpuscles, have proved to be erroneous.

The manufacture of anilin and of anilin colors affords the chief, and fortunately the only, facilities for cases of poisoning. The workers in such factories are most exposed to this danger. But cases of poisoning also occur, as Bergmann's case shows, with the red and violet (mauve) anilin colors, which sometimes contain large quantities of undecomposed anilin;—but generally only when, through some unlucky accident, large quantities of the poison get into the stomach. The medicinal use of anilin salts for epilepsy and other diseases, although as yet not very largely employed, has, so far as we know, given rise to no cases of poisoning. But the external use of hydrochlorate of anilin in two cases of psoriasis gave rise to poisoning, according to Lailler (loc. cit.).

We are decidedly of opinion that the affections caused by wearing articles dyed with anilin colors next the skin are not really properly attributable to anilin poisoning. The number of cases of pure anilin poisoning as yet placed on record is very small.

No trustworthy figures can be given as regards the poisonous or fatal dose of anilin in human beings.

Acute anilin poisoning is preceded in human beings by tolerably characteristic external symptoms, and all the cases hitherto published show a remarkable agreement in their principal features. The period at which the symptoms of poisoning begin varies, as it appears, according to the quantity of the poison taken and the mode of its ingestion. Whilst in some cases more than half an hour elapsed after the breathing in of the anilin vapors

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[1] *Ollivier* and *Bergeron*, Brown-Séquard, Journ. de Physiologie. VI.

before any symptoms of poisoning occurred, the action of the poison in one of the cases described by Mackenzie was extremely sudden. It was the case of a young man who was cleaning out an anilin vat, and was affected by the vapors; he was taken out of the vat in a half-conscious state.[1] In the case also of Knagges,[2] in which a workman broke a carboy of anilin, the symptoms of poisoning set in whilst the man was wiping it up with cloths. How long it takes for the poison to act when swallowed has not been determined with any certainty from the observations hitherto made. In Lailler's cases the general symptoms occurred in one and a half and four hours respectively after the application of the muriate of anilin to the skin.

The first symptoms consist in oppression in the head, nausea, vertigo, and headache. Lailler often observed vomiting. Gradually a sense of suffocation, and difficulty of breathing, with simultaneous somnolence, which in Mackenzie's case went on to loss of consciousness, occur—whilst Bergmann's patients retained their consciousness all the while. Pains in the extremities, and muscular weakness, with fibrillary cramps or convulsions, and anæsthesia of the skin, have been noted by almost all observers.

Amongst the objective symptoms, one of the most remarkable is the peculiar dark cyanotic coloring of the mucous membranes of the nose, ears, and nails. The rest of the skin shows a livid, bluish-gray coloration, and a lowered temperature. The pupils are not generally much affected. The pulse and respiration are quickened at first; the former at a later period grows slower, and is easily compressible. The breathing is labored and dyspnœal. General convulsions have not as yet been noted in human beings. All these symptoms generally vanish in the course of one, or at the most two days, without leaving behind them any very special disorders. Up to the present date, no case has ended fatally.

In the case of poisoning by anilin dyes, traces of these are found in the cavity of the mouth, in vomited matters, in the fæces, and in the urine, which in Bergmann's case was colored

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[1] Med. Times and Gaz. 1862. March. p. 239. Fletcher's case, quoted by Mackenzie in the same article, was not, as *Husemann* (Toxikologie. Sptb. p. 114) wrongly states, one of anilin, but of nitro-benzol poisoning.

[2] Med. Times and Gazette. 1861. I. 583.

bright red. Anilin itself is easily recognizable by its smell. Only Charvet[1] has described chronic poisoning by anilin. There were general nervous symptoms, vertigo, stupidity, muscular cramps and muscular weakness in the extremities, hyperæsthesia, anæsthesia, and neuralgic pains, which occurred epidemically along with gastric symptoms, amongst the working-people of the factory at Pierre-Bénite; and these symptoms all disappeared on removal from the poisonous atmosphere, without any further treatment.

The workers in anilin factories are said frequently to suffer from obstinate bronchitis, and they therefore guard against breathing in the vapors by keeping a damp towel in front of the mouth.

As regards the treatment of anilin poisoning, in the absence of special clinical experience on the point, and from the fact of no true antidote being known, we cannot lay down any special rules. Our treatment must be guided by the same principles which regulate that of other cases of narcotic poisoning.

CHAPTER IV.

POISONING BY CARBOLIC ACID ($\Theta_6H_6\Theta$; PHENILIC ACID, HYDRATE OF PHENYL).

Carbolic acid, one of the products of distillation from the coal-tar naphtha, so largely obtained in the preparation of gas for the purpose of lighting, has during the last thirty years attained great importance both as an article of commerce, as a medicine, and as a poison. The crude carbolic acid (often confounded with officinal creasote) is a brownish-red fluid, of the consistence of a thin syrup, of a penetrating, characteristic odor, and of a burning and highly unpleasant taste. But, of late more especially, crystallized carbolic acid is met with which occurs in colorless shining needles, which in large quantities have a faint

[1] Annales d'hygiène publ. Oct. 1863.

pink tinge, and have almost the same kind of strong empyreumatic unpleasant smell, though perhaps not quite so offensive as the crude acid. Both preparations are officinal. Even coal-tar naphtha itself (the oleum lithantracis of the pharmacopœias) deserves to be mentioned here, inasmuch as its medicinal, hygienic, and economic uses may sometimes give rise to cases of poisoning.

Carbolic acid as a poison, as a disinfectant, and as a medicine and surgical appliance, has been the subject of several treatises and of much study and experiment. We must confine ourselves here to the investigations on its action as a poison. Carbolic acid acts locally as well as generally. The local action is probably due to the strong affinity possessed by this substance for the constituents of the animal body, which is true, whether (in a concentrated condition) it simply abstracts water from the tissues, or whether it actually enters into combination with albuminous bodies. Five per cent. solutions of carbolic acid precipitate albumen, though Bill[1] states that the two substances are not chemically combined in this precipitation. Where the poison comes in contact with the surface of the skin, or of mucous membranes, a white scab forms, the thickness of which depends on the concentration of the acid. These effects are very similar to those of the weaker acids and other metallic caustics, and do not, therefore, need prolonged discussion.

The general effects of carbolic acid are dependent on its absorption into the blood. This absorption may occur in all the ways in which solutions are capable of being absorbed, and it would also seem as if the general action of carbolic acid may follow the breathing of air strongly impregnated with its fumes.

Opinions differ as to the removal and elimination of the substance from the fluids of the tissues (Säftemasse). There is no doubt that many observers have detected carbolic acid in the urine of animals and men poisoned by it. Hoppe-Seyler[2] also found it in the blood and internal organs of poisoned dogs. Lemaire's[3] statement, that carbolic acid occurs in the expired

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[1] See Virchow and Hirsch, Jahresbericht. 1872. I. p. 371.

[2] Pflueger's Archiv. V. 1872. [3] De l'acide phenique, etc. Paris. 1865.

air (of such cases), has not been confirmed by later researches, nor could Bill (loc. cit.) demonstrate it in the perspiration or in the fæces. From all this we may certainly conclude that a part of the poison introduced passes out again without suffering decomposition. Other observations render it also tolerably certain that some decomposition of this substance occurs in the blood, although we must consider Hoffmann's[1] view, that it undergoes complete combustion in the blood, as not established.

The dark-green, and often almost black color of the urine after standing some time, which often occurs when this poison is absorbed from the surface of a wound, is strikingly characteristic. It is seldom seen when the poison is taken internally. This symptom clearly depends on the presence in the urine of some product of decomposition of carbolic acid, the chemical nature of which has not been discovered. E. Salkowsky,[2] in commenting on this striking fact, inclines to the opinion that the decomposition occurs before the absorption of the carbolic acid, as it so rarely occurs from the internal use of this substance. This author believes most of the carbolic acid, applied either internally or externally, must be decomposed, because the quantities which can be demonstrated in the urine are always extremely small. The antiseptic qualities of carbolic acid only interest the toxicologist inasmuch as they demonstrate the poisonous character of carbolic acid as regards lowly organisms of both animal and vegetable origin.

Husemann and Ummethun,[3] and E. Salkowsky, have carefully investigated the general symptoms of poisoning which follow the absorption of this poison in both men and animals—the two former experimentally, the latter by the observation of a number of poisoning cases in the human subject. It must be premised that there is a very considerable discrepancy between the action of this poison on animals and in human beings. In the former there occur unmistakable symptoms of irritation of the medulla oblongata and of the spinal cord, which have as yet never been witnessed in human beings.

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[1] Beiträge zur Kenntniss der physiologischen Wirkungen der Carbolsäure und des Camphers. Inaug.-Dissert. Dorpat. 1866.

[2] Pflueger's Archiv. V. 1872.

[3] Deutsche Klinik. 1870, 1871.

These irritant phenomena partly concern the respiratory centres, and partly those for reflex action in the spinal cord. In frogs, E. Salkowsky observed, some time after the poisoning, consecutive to a stage of more or less paresis, clonic convulsions in the extremities, occurring and gradually increasing in severity, like those in strychnine poisoning, lasting for hours at a time. He also verified analogous affections in rabbits, in which what at first were only general muscular tremors, became general convulsions. Salkowsky refers the origin of these spasms to the spinal cord—their occurrence in various animals is confirmed by Husemann and Ummethun. These convulsions still happened when the brain and the prolongations of the spinal cord (medulla, etc.) were severed (by section) from the spinal cord itself, and also when the arteries conveying blood to the limbs were ligatured. It could not, therefore, be said that the convulsions were due to asphyxia.

The disorders of respiration consist in a very considerable increase of the frequency of breathing, and in its becoming very superficial. Fatal doses bring on dyspnœa at the last, and manifestly lead to death by paralysis of respiration. The first acceleration of respiration is not entirely prevented by section of the vagus, although this operation is of unmistakable efficacy. On the other hand, carbolic acid is able to increase the number of respirations in an animal whose vagi have been previously divided. Salkowsky therefore believes that this poison not only affects the respiratory nerve-centres, but also excites the pulmonary terminations of the vagus. The organs of circulation are less affected by carbolic acid. The frequency of the beats in the frog's heart gradually diminishes to about half, whilst the convulsions go on increasing. We shall return to the symptoms in human beings by and by.

The gastro-intestinal symptoms produced by the local action of the poison in the stomach and bowels do not need any minute description.

In the intensity of its action, carbolic acid belongs to the strong poisons, though not to the very strongest of all. On an average several decigrammes (a decigramme=$1\frac{1}{2}$ grain nearly) are required to kill even very small animals, so that this poison

is considerably inferior in strength to the more violent alkaloids, to prussic acid, to sulphuretted hydrogen, and to the corrosive mineral poisons.

As regards the susceptibility of various classes of animals, and the poisonous and fatal doses in each class, we must refer to the often-quoted monographs of Lemaire, Husemann, Ummethun, Salkowsky, and others.

The very varied uses of carbolic acid, both in medicine and surgery, and its economic and hygienic uses of late years, have given rise to a large number of poisoning cases in human beings. The cases hitherto observed, therefore, belong partly to the domain of economic or technical poisonings, partly to so-called medicinal ones, and in some few cases it has been taken with suicidal intent. Most of the medicinal cases have arisen from the use of carbolic acid as an external application, either for skin-diseases (as, for example, scabies, etc.)—in which it was rubbed into the uninjured skin (cases by Koehler and Machin)—or by its application when insufficiently diluted to open wounds, suppurating surfaces, and abscesses. Sandwell also states that water-closets in which it has been used for disinfection, when they have been imperfectly cleansed, have given rise to symptoms of poisoning —chiefly consisting of pains in the gluteal region. Very severe symptoms were caused in two cases (those of Pinkham and Michaelis), through clysters of carbolic acid used against intestinal worms—and these confirm the statements of Husemann and Ummethun, that in their experiments on animals the poisonous action occurred very rapidly when the poison was applied to the rectum. England has furnished by far the largest number of cases: 26 out of 33 such cases recorded were in England, and only 7 in Germany, France, and Switzerland; 21 were in males, 10 in females; 26 ended fatally, and 7 recovered; 2 only were cases of suicide; 11 of medicinal application; in 20 an accident was the cause. The poison was taken internally in 22 cases, whilst in 9 the symptoms followed its external application. Children exhibited a great degree of sensitiveness to the poison; but in this, too, individual peculiarities played a part. The poison naturally acts with more rapidity and energy on an empty stomach than on a full one.

As regards the fatal dose, we cannot fix any definite limits. In applications to the skin, very severe symptoms have occasionally resulted from relatively very small quantities of the poison. As regards internal use, Husemann considers eight grains as a dangerous dose. In most of the cases of poisoning it is not easy to fix the quantity of the poison very definitely. The doses determined as poisonous in animals are, it is easy to understand, not applicable to the case of human beings.

From the cases of poisoning by carbolic acid which have been recorded, we select the following as being those in which the fatal dose and other circumstances are pretty accurately recorded:

Observer.	Subject of Poisoning.	Dose.	Result.
Jeffreys & Hainworth	Man aged 56.	℥ i.	Death after 50 minutes.
Ogston.	" " 47.	℥ i.–ii.	" 13 hours.
Zimm.	A soldier.	30–40 grm.= 465 to 620 grs.	" 60 "
Wiltshire.	Typhus patient (æt. 19).	℥ ss.	" 2 days.
Harley.	Man aged 47.	℥ i.	" 5½ hours.
Sutton.	" " 43.	℥ i.	" 1½ "
Pinkham.	Child aged 1½.	2 teaspoonfuls.	" 12 "
Way, J.	Woman aged 35.	℥ viii.	Died suddenly.
Brabant.	" " 44.	℥ i.	Death after 50 minutes.
Russel.	Girl aged 10.	℥ ss.	" 85 "
George.	?	℥ i.	" 30 "

An ounce of concentrated carbolic acid may, therefore, under all circumstances, be regarded as a very dangerous, if not absolutely fatal dose, although we cannot dare to say that even, smaller quantities (*e. g.*, one tablespoonful or half an ounce) may not produce fatal symptoms. The results of this inquiry are approximatively accurate, and enable us rather to say what will, than what will not, be likely to prove fatal.

The symptoms of poisoning by carbolic acid in human beings offer the following characteristic features. In acute poisoning, with large quantities of the poison, loss of consciousness and of voluntary movements sets in, as a rule, in a very few minutes. Those poisoned sink into a comatose condition, in which generally sensibility and reflex movements are completely abolished.

The breathing is described as stertorous by most observers, or, if consciousness is not entirely lost, as very laborious and dyspnœal. Well marked general convulsions, up to the date of this, have never been developed in human beings, but are scarcely ever absent in experiments on animals. Death succeeds and terminates this comatose condition without any other very striking symptoms. We find a high degree of contraction of the pupils, which are insensible to light, noticed as an almost constant symptom. The skin is cool, covered with sweat, and exhibits a livid color. Urine and fæces are obstinately suppressed.

Vomiting is one of the most constant symptoms, and occurs principally, it seems, at the beginning of the poisoning. In the earlier stages of the poisoning, the pulse is generally strikingly slow; later on it is generally much quickened. The repeated filling of the mouth with foam, observed in Jeffreys' and Hainworth's cases, may be ascribed to salivation, which has been observed in most cases of poisons which kill by asphyxia.

We have already noted the condition of the urine sometimes met with—and although this dark coloration is due, as a rule, to the external application, yet it does undoubtedly occur in cases of poisoning by the internal use of carbolic acid also, as is indubitably proved by the cases of Ogston, Zimm, Wiltshire, and Ferrier. It might therefore be well, in all doubtful cases of carbolic acid poisoning, accompanied with retention of urine, to use the catheter as a means of diagnosis. Albuminuria has occasionally been noted, but is not a constant symptom of poisoning by carbolic acid. In a few cases it has been accompanied with pains in the region of the kidneys. The local action of the poison is often very manifest, when it is swallowed; for, immediately after the poisoning, it is common for violent pains to occur in the course of the œsophagus, below the sternum, and in the region of the stomach. The vomiting also which occurs in an early stage may be attributed to the local irritation, though it is right to mention that it also occurs in cases of poisoning by the external application of comparatively small quantities of the poison. The nervous symptoms which succeed render any special extension of these pains in the stomach and abdomen impossible.

The whitish coloration of the mucous membrane of the mouth and throat, and the scabs or crusts due to the caustic action in the neighborhood of the mouth, or on other parts of the skin, may serve as aids to diagnosis. In less severe cases of poisoning by carbolic acid, those affected complain of headache, vertigo, nausea, want of appetite, and other similar, but little characteristic phenomena. Zimm's case shows in a very striking manner that in this sort of poisoning, particularly in a state of coma, and of total reflex paresis, it is very easy for part of the poison to get into the air-passages; no doubt in this case the frequent vomiting led to this unpleasant complication. The autopsy in this case revealed double pneumonia.

The peculiar urine and the firm adhesion of the peculiar and not easily mistaken smell of carbolic acid to the clothes and person of the poisoned must be regarded as diagnostic points of considerable importance in cases which might be otherwise doubtful.

Carbolic acid poisoning, particularly when large quantities are taken, usually runs a very rapid course, and is very rarely protracted. All the hitherto noticed fatal cases have proved so in the course of the first twelve hours—some, indeed, after only a few minutes. Even when recovery occurs this is usually sudden, and without leaving behind it any remarkable disorders or noteworthy complications.

As regards the results of anatomico-pathological (post-mortem) investigation, we must again lay special stress on the smell of carbolic acid, which pervades and adheres to the contents of the digestive canal, the glandular organs and their secretions (urine), and in cases of poisoning by a large dose is hardly ever absent. The remaining changes offer nothing very remarkable. We can scarcely lay much stress on that quality of the blood on which Husemann so insists, viz., that it is very thin and dark-colored, and coagulates badly—at least as regards human beings. Apart from the very precarious and doubtful nature of the symptom itself, it does not appear that, in cases of poisoning by carbolic acid in human beings, the quality of the blood has been at all uniform. Indeed, in several of the recorded accounts of postmortems, we find express mention of extensive clots in the heart

and large vessels (Ogston, Zimm). The appearances on the mucous membranes of the digestive organs are of far more importance—the whitish color, the hardness of the epithelial coating, and the loss of substance—but they are such as occur also in cases of poisoning by other dilute acids. A black color of the kidney, after long exposure to the air, has only been noted in one case (Barlow's) in the human subject, and has been found in animals by Husemann, although not constantly.

As regards the treatment of carbolic acid poisoning, we have very little clinical experience of a useful kind to guide us. The stomach-pump was used with considerable success in one case by Mosler; and there can be no doubt that it may be useful in other cases for the removal of large quantities of the poison from the stomach, if its use is not counterindicated by a suspicion of strong corrosion or erosion of the stomach. Husemann and Ummethun have instituted numerous experiments in order to discover antidotes, and after proving that a number of substances (glycerine, oils, alkalies, etc.) are useless, saccharated lime (calcaria saccharata) proved to be the substance which most nearly corresponded to the requirements of a chemical antidote for carbolic acid. The compound of lime and carbolic acid is easily soluble and not poisonous. The use of lime-water itself is not practicable, on account of the great quantity required in order to neutralize the carbolic acid in any given case of poisoning. Of course the antidote is only applicable in cases of poisoning by the internal use of carbolic acid. The saccharated lime may easily be given in watery solution, or, if needs be, by an œsophageal tube. Whenever possible, this procedure should always precede the application of the stomach-pump.

The nervous symptoms in carbolic acid poisoning may also necessitate a symptomatic treatment; thus, in extreme coma, cutaneous irritants, artificial respiration, electricity, and all the other aids and appliances recommended in other cases of narcosis.

CHAPTER V.

POISONING BY NITRO-GLYCERINE.

The substance known as blasting-oil (Sprengöl), *nitro-glycerine* or *glonoïn* ($C_3H_5O_3(NO_2)_3$), is an oily, very slightly volatile, but extremely explosive liquid, which is shown by numerous experiments, agreeing with one another, to be a poison, both to various classes of animals and also to human beings. But, so far as we know from the experimental and other cases of poisoning which have occurred, its action as a poison is far more intense in animals than in the human subject.

As cases of poisoning by nitro-glycerine are excessively rare, we shall not discuss the very copious materials collected with so much care by Husemann,[1] but the following observations may serve as a practical guide:

Nitro-glycerine is very slightly soluble in water (only 0.25 per cent., according to Nystroem). Its poisonous effects succeed its introduction into the mouth, as well as its application to the sound skin. As regards its elimination and its behavior in the system, nothing very precise is known. It has been supposed that nitro-glycerine leads to the formation of nitrogen monoxide (Stickoxydul) in the blood (Onsum[2]), or even prussic acid (Nystroem[3]), and that its poisonous action is due to some such decomposition.

The effects of nitro-glycerine on frogs consist in tetanic convulsions, followed by general paralysis. Even mammals get convulsions, besides dyspnœa, quickened pulse, mydriasis, and general paralysis. In frogs no convulsions occur if the cerebrum be removed previous to the poisoning.

In human beings it appears that very small doses of nitro-glycerine cause severe and long-persistent headaches, associated with an unpleasant knocking or hammering in the temporal regions, considerably increased by any movements of the head.

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[1] Schmidt's Jahrbücher. 1866.

[2] Quoted by *Husemann*, loc. cit.

[3] Reference as before.

Heaviness in the head, clouds before the eyes, vertigo, quickening of the pulse, and palpitation, and a feeling of heat in the face have been noted as special symptoms of poisoning. Larger doses are said to cause dyspnœa, oppression in the chest, lassitude, muscular weakness, and stiffness in the muscles of the jaw. Onsum[1] lost consciousness after a dose of ten drops of nitro-glycerine; on awaking out of this unconsciousness there occurred severe headache, and general muscular tremors. There were no true convulsions. Nitro-glycerine also has a local action. When swallowed it causes burning in the throat, pains in the epigastrium, hiccough, nausea, vomiting, and sometimes colicky pains, with diarrhœa.

The great majority of cases of poisoning by nitro-glycerine terminated favorably, although considerable alarm was felt at first on account of symptoms such as general paralysis being present. Yet it is usual for severe headache to be left for several days. In one of Husemann's[2] cases the general paralysis lasted till the evening of the next day. According to Nystroem, three fatal cases of poisoning by nitro-glycerine have occurred in Sweden. Death without convulsions succeeded severe dyspnœa, with cyanosis in the condition of coma. Hyperæmia of the cranial contents was found at the autopsy. The clinical materials being so scanty, it is not easy to lay down rules for the treatment of poisoning by nitro-glycerine. Morphia is without any action as regards the relief of the headache caused by this poison. There is as yet no known antidote. Accordingly the treatment, at present, must be purely expectant or symptomatic.

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[1] Loc. cit.

[2] Deutsche Klinik. 1867. 18, 19.

THIRD PART.

Poisoning by Tainted Articles of Diet.

CHAPTER I.

SAUSAGE-POISONING. BOTULISMUS. ALLANTIASIS.

Amongst the maladies which owe their origin to the use of articles of nourishment from the animal kingdom which are undergoing decomposition, there are some which are designated as cases of poisoning, and studied by toxicologists on account of their peculiar and sharply defined symptoms, which are in part those of narcosis, and on account of their singular and generally fatal course and termination. Yet it is no more possible now than it was eighty years ago to discover any specific poison in such cases, or to accurately determine the chemical nature of the poison supposed to be present. All the numerous hypotheses and suspicions, both of former times and of more recent date, as to the nature of this poison, have, one after another, been proved erroneous.

It must be clearly understood that the existence of any preformed poison in the foods which cause the illness is itself, as yet, only an hypothesis; for, on the one hand, we cannot quite dismiss the hypothesis that lower organisms of a fungoid nature may be implicated in the causation of the malady; whilst, on the other hand, there is a strong suspicion that the injurious substance which acts as a poison may be developed for the first time within the human body out of the tainted meat. And, unfortunately, the darkness which thus invests the whole subject cannot be cleared up by experiments on animals, for the door of research

in this direction seems barred by the fact that the substances concerned only appear to cause morbid symptoms in human beings, and can be partaken of by the animals generally used in toxicological researches (dogs, cats, etc.) without their suffering any inconveniences. The study of the true nature of sausage-poisoning, and of the opinions which have been formed upon it, is so far of interest as exhibiting the present standpoint of our chemical knowledge and of pathological opinion. The subject is exhaustively and elaborately discussed in "Husemann's Toxikologie," and also by Mueller, in a recent *résumé* of all that relates to sausage-poisoning and the like,[1] to which we refer for details. Only the leading features can be indicated here.

As chemical analysis has, in a large number of the cases, most positively settled the fact that no metallic poisons, such as arsenic, copper, or the like, were present, these could not be the real cause of the sausage-poisoning. We are therefore driven to look for the true cause of the poisoning in the organic substances of which they were composed. As these comprise a great variety of different kinds of meat and fats, sometimes smoked or cured, and sometimes not so treated—blood, liver, bacon, pork, etc., etc.—and as all and each of these have produced symptoms which are practically identical, and only differ in the intensity of the symptoms, the opinion that processes of decomposition, or the products of decay, are the true cause of the symptoms, has become accepted as very probable. But since the ordinary products of animal decay do not produce the same specific action in human beings, there has been started a fresh hypothesis of a "modified or peculiar putridity" to account for the action of the sausage-poison; an hypothesis which may serve at least a temporary purpose.

The literature of sausage-poisoning does not date any further back than the first ten years of the present century; and general attention was first attracted to it by the exhaustive works of Justinus Kerner[2] on the remarkable disease caused by this poison. We owe to him a good account of the earlier cases. Kerner believed that all the symptoms were due to a "fatty acid," which he considered the active poison

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[1] Deutsche Klinik. 1869, 1870.

[2] Neue Beobachtungen, etc. Tübingen, 1820; und Das Fettgift. Tübingen, 1822.

in the sausages, and he made a number of experiments on dogs and other animals, in which it would appear that the fatty acid artificially prepared by him excited symptoms similar to those caused by the poisonous sausage. Unfortunately, however, the reading of this lecture makes one suspect that Kerner frequently introduced his poison into the larynx, and thus produced the aphonia which he considered a pathognomonic symptom of the sausage-poisoning. But authors long entertained the opinion, founded on the acid reaction of the poisonous foods, that they contained a poisonous acid, combined with some volatile substance. This opinion was first shown to be incorrect by Schlossberger,[1] who suspected rather that organic bases were present in the sausage-poison. Hoppe-Seyler, however, the last chemist who has analyzed a poisonous sausage, failed in demonstrating any organic bases in it, and accordingly, at the present moment, the results of all chemical investigations into the sausage-poison are purely negative.

And as nothing positive can be said as to the nature of the poison, except that it is very probably the result of slow putrefaction of animal substances, so also the true nature of the poisonous process, the pathology of it, is also highly obscure, differs widely from all other kinds of poisoning, and cannot well be compared with any of them.

It appears to us to be characterized by the tedious course of the poisoning, extending over many days, and sometimes weeks; and that these point to processes going on in the blood, which do not occur in other kinds of poisoning, in which we simply have to do with the absorption and elimination of a foreign body from the system. Although symptoms of disorders of the digestive tract are scarcely ever absent, yet the whole disease does not at all resemble a simple attack of gastro-enteritis. And the results of post-mortem investigation in cases of sausage-poisoning forbid our entertaining the opinion that the injurious agent has a local action analogous to that of other irritant and corrosive substances. So also in the domain of the nervous system, the symptoms are just as little comparable with those of pure narcotic poisons, if we take them in their totality, and not separately, and especially if we regard the long persistence which they exhibit in so striking a manner. There are some of the symptoms which make us suspect that a lasting change in the nutrition of the nerve-centres occurs, just as in diabetes mellitus, for example. And just in the same way the disorders of the gene-

[1] Archiv für phys. Heilkunde. 1853.

ral health, the persistent anomalies of nutrition which have been observed in the stage of convalescence, indicate an influence on the part of the poison on the general processes of nutrition in the body. A comparison of the symptoms as a whole in this way leads to a far more correct judgment, than if we take only one or two of the symptoms, which may easily lead to a comparison with conditions which are absolutely dissimilar. For example, the observation of the mydriasis and of the spinal symptoms has led to a parallel being drawn between belladonna- and sausage-poisoning, not to mention other comparisons which are far more adventurous. An accurate study of the recorded cases and symptomatology of the sausage-poisoning will not allow us to draw any other than these somewhat negative conclusions. The notion entertained by so many authors that the sympathetic nervous system is specially implicated rests on no more solid basis of facts than many other hypotheses about this condition. At least we fail to discover any symptom fairly attributable to the sympathetic. The implication of the sympathetic system of nerves is a relic of the time when all inexplicable pathological phenomena were set down to the sympathetic nerve, which was thus a sort of convenient scapegoat, because the functions of this nerve were not at all known at the time. We must beware lest we ourselves fall into a similar mistake by making abstractions from the known symptomatology of this disease.

Husemann and Mueller rightly insist that sausage-poisoning has been frequently confounded with more or less widely different conditions which were due to other noxious things contained in articles of animal food. The most important of these is trichinosis, which appears several times to have given rise to a mistaken diagnosis of botulismus. Nor should the illness arising from the meat of decomposing or diseased animals be identified with sausage-poisoning. It may, however, be combined with this and considerably modify its typical and usual symptoms. The conditions generated by putrefying substances are more akin to typhoid fevers—are perhaps actually a kind of typhus. In the remarks which follow we shall consider typical sausage-poisoning only.

The etiology, actual occurrence, and the extension of this form of poisoning by sausages are as peculiar as its pathology. An overwhelming proportion of the cases of poisoning have occurred in the kingdom of Würtemberg and the adjacent Swabian parts of Baden. The Würtemberg Black Forest and the neighborhood of the so-called Welzheimerwald are, according to Kerner and Paulus, the districts most commonly affected. Only a few cases occurred in the adjacent district of Bavaria. In all the rest of Europe, in spite of the general attention excited by the writings of Kerner, Schlosser, and other writers, only solitary cases of this poisoning are known. The following statistical account is taken from Kerner, Husemann, and the careful compilation of Mueller. In Kerner's first publication there were 76 cases (of which 37 were fatal), and some of these dated back to the year 1789. In his second publication (dated 1822), he adduced 155 cases (with 84 fatal ones). In 1827 there were 234 known (with 110 fatal), and in 1853, about 400 (with 150 fatal ones) had been published. Of late the frequency of cases of sausage-poisoning, even in Würtemberg, seems to have considerably decreased. Whilst in the years 1832–1862, according to Faber,[1] 82 cases occurred in that country only, of which 19 ended in death, we could discover in the literature of 1866–1874 only 15 more, of which 12 belonged to Würtemberg, 3 to Saxony (Dresden), and only one ended fatally. It does not seem likely that either less attention would be given to those cases, or that they would be less likely to be published of late years. Of the cases of sausage-poisoning occurring elsewhere than in Würtemberg, the most recent is that of Niedner (Dresden).[2] In Westphalia (Kreis Soest, Olpe) from 1820 to 1830 there were 18 cases; in 1853, 1 case. In Lippe-Detmold, 14 cases in 1835; 1 in England in 1860; and 2 cases altogether in France.[3] In the larger towns, botulismus occurs extremely seldom; nearly all the cases have been in country people, and in the earlier months of the year.

It is not surprising that much care has been given to diligently seek the reason for this peculiar predisposition of the

[1] Würtemb. Corr. Bl. 1854. [2] Berliner klin. Wochenschrift. 1866.
[3] See *Mueller*, loc. cit.

Swabian districts to sausage-poisoning; and no other explanation can be found than faulty methods of preparing the sausages. All other explanations have broken down, and need not be refuted here. Mueller mentions the following points in which the Swabian method of preparing sausages is favorable to the origination of the poison:

1. The meat used for the sausages is often insufficiently cooked.

2. A number of substances not suitable for sausages are employed in their manufacture, such as milk, flour, meal, brains, onions, and herbs like bennet-root (Nelkenwürzel, Geum urbanum), too large pieces of fat, etc.

3. The proportion of liquids to solids in the sausages is a wrong one.

The peculiar method of smoking or curing the sausages practised in Swabia also has disadvantages of its own. The smoking places are generally very badly ventilated, and instead of the sausages being hung high up in the chimney, where the smoke is thin and cool, as in other places, they are hung immediately over the fire, in the hot smoke. Moreover, in Swabia, they do not, as elsewhere, keep up a gentle or small fire all night, so that in winter it is quite possible for the sausages to freeze at night and be thawed again in the daytime, and this condition is just the very thing to favor the decomposition of the sausages. And lastly, it is said that in Swabia it is common enough for people to add bullock's blood, or the blood of sheep, or even of goats, several days old, to the sausages—and the latter are not kept in proper, cool, airy rooms, but in wooden boxes or chests. Blood-puddings and liver-sausages most commonly give rise to the poisoning cases, but they have been known to occur after the use of beef-sausages, pork-sausages, and other kinds. One kind, known in Swabia under the name of "Blunzen," consisting of pigs' stomachs filled with sausage-meat, seem to favor the production of the poison by their great thickness, since it is easy to see that the perfect "smoking" or "curing" of so thick a mass can only take place slowly, and it is quite possible for the interior portions of the sausage to undergo a poison-generating process of putrefaction before they can be penetrated with the

antiseptic constituents of the wood-smoke. All observers agree in considering the interior portions of the sausages as the most poisonous; some say the only poisonous part is the inside, and there are even cases on record of poisoning, in which only those who ate the tainted inner parts became ill.

All the authors on the subject agree in giving the following as the characteristics or outward signs which indicate that a sausage is poisonous:

The putrefied sausages, or portions of sausage, when recently cut across, have a dirty, grayish-green color, and a soft cheesy-like, smeary consistence. They diffuse a very disagreeable smell of putrid cheese; the taste is disgusting, and sometimes causes smarting or soreness in the throat.

Sausage-poisoning occurs rarely in solitary cases; it generally attacks whole families which have simultaneously eaten the decomposing food. The intensity of the attack seems to depend both on the quantity of the poison ingested and on individual susceptibility to the poison. This susceptibility varies a good deal, and a careful consideration of the recorded cases does not permit of doubt on this point, though constitution, age, and sex all play their part. The asserted immunity of pregnant women has never been satisfactorily disproved by the occurrence of cases in such. Mueller thinks that the poison occurs in different sausages in different degrees of concentration (rather, perhaps, of potency). The course of botulismus is, as a rule, subacute, and very commonly chronic. Cases running a very sudden course are rare. Under all sorts of circumstances poisoning by sausages is more tedious than most cases of poisoning by other well-known poisons. Even a fatal termination, as a rule, seldom closes the sickness in less than five or six days.

The first symptoms of poisoning occur in the majority of cases in from eighteen to twenty-four hours after taking the injurious food. The extreme limits of the stage of latency are from one hour to nine days. Mueller has carefully collected 140 cases with reliable statements on this point. Accordingly, we find that a latent stage of less than twelve hours is just about as common as one of more than twenty-four hours. In 83 out of

the 124 cases the first symptoms occurred after twelve hours, and before the second day after taking the poison.

We agree with Husemann in considering that the division of the symptoms of poisoning into stages is superfluous. Even Mueller's proposed division into a stage of invasion or excitement, and one of paresis or paralysis, cannot be maintained, since the gastro-intestinal symptoms do not invariably precede the nervous symptoms, but often enough both occur simultaneously. As a rule, however, the sufferers complain at first of general discomfort and nausea, pain and sense of weight in the region of the stomach, quickly followed by diarrhœa and vomiting. Very often colicky pains, which disappear and then return again after a while, are the first symptoms, the severer symptoms not setting in till some days after. Sometimes also the scene commences with violent vomiting and retching, vertigo, cloudiness of vision, and difficulty in swallowing; lastly, the gastro-intestinal symptoms may be entirely absent, and the difficulty in swallowing, disordered vision, muscular weakness, and general prostration constitute the disease.

Dyspnœa and feelings of suffocation (precordial anxiety) have been especially mentioned as being not infrequently some of the early symptoms.

Although this condition is often protracted for several days with indefinite disorders, partly gastric and partly nervous, during which the patient very commonly goes about his usual business or occupations, in the majority of cases there is very soon so much weakness that they cannot long keep out of bed. The vomiting, often so troublesome at first, and sometimes, though rarely, persisting in the form of tormenting feelings of choking (Würgbewegungen) and retching, the diarrhœa and the colicky pains all recede into the background, and give place to the nervous symptoms. These are in part of a general nature, and in part limited to special regions and nervous tracts. Consciousness and thought, and all the special qualities of soul which are called the higher faculties, remain, with but few exceptions, intact all through the whole course of the attack, although giddiness, headache, and an apathetic comatose condition in many cases indicate anomalies in the functions of the brain.

Any definite paralysis of the voluntary muscles or of sensation has never been noted, any more than clonic or tonic spasms. It is rather extreme muscular weakness—which limits to the most minimal degree the exercise of the voluntary muscles, but never till just before death renders it impossible—than an actual paralysis. Any marked disorders of sensation are also absent, although the sensibility of the tips of the fingers is said to be diminished, and sometimes the patients complain of crawling and painful feelings in the extremities and back. Moreover, it is expressly declared that sleep generally occurs in a perfectly normal way.

The visual apparatus suffers in a very extraordinary way in sausage-poisoning. The first complaints of the patients point to diminished visual power, and are sometimes complained of as a cloud or mist before the eyes, sometimes as sparks, and sometimes as mere weakness of sight. Very soon there is double vision, with diminished acuteness of vision; the powers of the ocular muscles are greatly limited, and sometimes quite abolished, and one of the most constant symptoms is paresis of the levator palpebræ superioris (ptosis). Very commonly also the nervus oculo-motorius is implicated, and the external rectus also paralyzed. The pupil is dilated, but does not become quite insensible to light; finally, the faculty of accommodation seems considerably lessened. Indeed, in some cases total blindness has been observed.

Whilst, then, all the remaining nerves of sensation preserve their faculties unimpaired, some of the nervous apparatus subservient to respiration appears to undergo very extensive changes. This is indicated by the more or less perfect aphonia of those poisoned, with the varying degrees of general difficulty of breathing, and the frequently noted tormenting, and sometimes croupy cough, which, however, may very often really stand in close connection, as to their true cause, with the difficulty of swallowing (dysphagia), so that when nourishment is being given, whether food or drink, a portion may easily find its way into the air-passages.

The disorders in the domain of the glosso-pharyngeal nerve are expressed in the almost pathognomonic symptom of dys-

phagia, which sometimes culminates in perfect aphagia or complete inability to swallow. The tongue also appears more or less hampered in its movements, and speech becomes stammering and unintelligible.

The remarkable dryness of the mouth and fauces indicates anomalies in the secretion of saliva. The mucous membrane of the mouth and pharynx shows either speckled or diffused redness, sometimes one, sometimes the other; sometimes there are also swelling, and aphthous formations; the tongue has a whitish coat. Lastly, the constipation which is constantly observed in the later stages, and the less constant retention of urine, must be considered as nervous symptoms, although little definite can be said as to their mode of origin. The hard scybala, sometimes broken down by energetic clysters, or discovered post-mortem in the large intestine, render it highly probable that the secretion of the various intestinal glands is considerably inhibited in sausage-poisoning.

The signs of need of nourishment are often rather more manifest than is usually the case; some patients complain of hunger, the above-named difficulty of swallowing making it almost or entirely impossible to take nourishment. Thirst is mentioned only in a few cases.

The organs of circulation appear greatly weakened in their functions. The pulse, which at first is feeble and slower than usual, vanishes sometimes altogether. Indeed, authors maintain that it is impossible in the later stages to make out the sounds of the heart. Accordingly we find the skin pale, and the mucous membranes of a livid color. The failing energy of the circulation is shown by the coldness of the skin—but no thermometric observations of the temperature are recorded. The rapid decrease of the nutrient powers, the great emaciation, are the unavoidable result of the want of power to take food, and the disordered functions of the digestive organs. The organism, thus condemned to hunger, may, however, last a remarkably long time, unless the introduction of food into the air-passages, by causing œdema of the lungs, brings life to a more rapid end. As a rule, notwithstanding the long-continued depression of the circulation, there is not generally any œdema, with the exception of a few

cases in which the formation of marasmic thromboses may give rise to it. Death generally follows without any specially violent symptoms; it is preceded by a comatose or soporific condition, sometimes with slight general convulsions, from one day to three weeks after the poisoning.

Those cases which end favorably are often marked by a very slow convalescence, in which the disorders of vision, and the difficulty of swallowing often persist for a long time, and the patients' strength returns to them very slowly and gradually. In some cases desquamation of the epidermis has been noted.

We quote from Mueller the following statistics as to the mortality, and the time at which death occurs.

Of 48 fatal cases, of which we have accurate accounts,

4 persons died a short time (?) after taking the poison.				
2 persons in the first 24 hours.				
6 persons accordingly on the 1st day.				
2	"	"	"	2d "
4	"	"	"	4th "
3	"	"	"	5th "
2	"	"	"	6th "
8	"	"	"	7th "
5	"	"	"	8th "
3	"	"	"	9th "
8	"	"	"	10th "
2	"	"	"	13th "
1	"	"	"	14th "
1 person after three weeks.				
3	"	longer illness (?)		
48 persons in all.				

From the figures given above (page 541), as the result of various collections, the general mortality appears to fluctuate between 23.2 and 54.2 per cent., and of late years the mortality is decidedly less than it was formerly.

The tolerably copious materials which are now possessed by the pathologist in regard to alantiasis only allow of one safe

conclusion being drawn, which is, that this form of poisoning furnishes no post-mortem appearances diagnostic of it, and from the morbid anatomy alone, therefore, no conclusions can be drawn as to the real cause of death.

Putrefaction occurs very slowly after death from sausage-poisoning. But Mueller's researches show that even this symptom is far from being a constant one, for out of 48 post-mortems carefully recorded, in 11, or nearly 25 per cent. of all, it is expressly mentioned that there was a very strikingly rapid development of putrescence. Post-mortem rigidity was just as often absent as present. The most common symptom was hyperæmia of the œsophagus, pharynx, stomach, and intestinal canal. The mouth was generally noted as very dry, and hard and dried-up fæcal masses were found in the lower portions of the intestinal canal. The liver and brain in the majority of cases are described as (? abnormally) full of blood. The lungs also are generally gorged with black blood; œdema and hepatization are only mentioned exceptionally. The bronchial mucous membrane often shows a dark and sometimes petechial reddening, and croupous membranes have once or twice been found in the trachea. When we consider how carefully and skeptically the records of congestion or fulness of blood in various organs are now scrutinized, and how little importance is attached even to the most accurate statements on these points, we must perforce consider these results as negative. The depressed state of the circulation renders accumulation of blood in the abdominal viscera extremely probable.

As the sausage-poison manifests its power only slowly and tediously, *the treatment of recent cases by the administration of energetic evacuants* seems especially indicated. These must be chosen according to the particular case. Hitherto all other therapeutic rules and attempts in the later stages have proved utterly useless; and we need not, therefore, uselessly fill space with the details. Theoretically there can be no objection to the use of counterirritants in the later stages. But it must be remarked here, that in the later stages of alantiasis the most drastic purgatives lose their power, and the only way in which the bowels have been sometimes relieved has been by the use of

clysters. In the convalescent stage, the treatment must be tonic and watchful. It is to be hoped that the more accurate knowledge of the dangers arising from improper methods of preparing sausages may gradually arouse the rural population from its apathy, and thus the occasion for this frightful form of poisoning may cease. This hope is, in fact, justified by the great decrease in the number of cases of sausage-poisoning during the last decennial period.

CHAPTER II.

POISONING BY POISONOUS FISH.

The question whether any species of fish is in existence, the use of which is capable, under all sorts of conditions, of setting up indubitable symptoms of poisoning in human beings—in other words, the question whether any fish is poisonous *per se*—though strongly contested, cannot be absolutely denied. All we can certainly say is, that no such fish is known at the present moment. On the other hand, the number of species of fish which are commonly regarded with suspicion as poisonous is very great. Nor can it be denied that, under special conditions, fish, which in themselves may be perfectly harmless, may become poisonous. Only those cases of fish-poisoning which fall under this latter category can properly be included in a toxicological hand-book, for no other cases have been properly studied, or are sufficiently known. As regards fish suspected of being poisonous, all that we could do would be to insert a long catalogue of, for the most part, very doubtful notices from travellers' descriptions, old books of natural history, and the like, of which little or no use could be made from either a practical or a scientific point of view—and we therefore forbear.

Autenrieth,[1] in a monogram on fish-poisoning, has catalogued some seventy suspicious kinds of fish, with references and notices belonging thereto—and to this we must refer the reader

[1] Ueber das Gift der Fische. Tübingen. 1833.

curious in such matters. There is also a catalogue in v. Hasselt-Henkel's [1] Toxicology, from which we extract only the general statement, that they are almost exclusively sea or salt-water fishes, and that of these the osseous fishes living in the tropical seas of the East and West Indies, are the ones which are most commonly regarded as poisonous. Amongst the Chinese and Japanese, the poisonous nature of some fishes, especially of the so-called sting-belly (*Tetrodon ocellatus*), is so generally and certainly believed, that those weary of life have even used them for suicidal purposes.[2] The poisonous nature of certain fishes is indicated by the names which they have popularly received (Betrayer, Purging-fish, Poison-fish, etc.).

The more important clinical cases of fish-poisoning have all been traced to a few kinds of fish whose flesh is extensively used, particularly in the department of Volga in Russia. These fish are the various *sturgeons* (the great sturgeon or beluga, *Accipenser huso*, and the sterlet or *Accipenser ruthenus*, and *Accipenser sturio* or British sturgeon). Since these fish in themselves are not the least poisonous, and serve thousands of people for their daily nourishment, we must accordingly, as in the case of sausage-poisoning, with which these cases show some analogy, have to do simply with processes of decomposition (catalysis), which, being favored by careless methods of preparing the food, give occasion to the generation of poisonous substances. Scarcely anything worthy of note has been published regarding fish-poisoning, with the exception of these Russian cases. But then these singular cases occur with tolerable frequency, and the geographical domain of the fish-poison is far wider in extent than that of the sausage-poisoning. Accordingly, when Sengbusch, in the two first years of the *Medicinische Zeitung Russlands* (1844–45), had drawn the attention of medical men through repeated notices to the then little-known circumstances, it was investigated at the instance of the Russian government, in 1857, by A. Owsjannikoff,[3] and thoroughly discussed in the successive papers of Koch,[4] Berkowsky and Kieter.[5] The practical results

[1] Zweite Auflage. Braunschweig. 1862.
[2] *Autenrieth*, loc. cit. p. 50.
[3] Medic. Zeitschrift Russlands. 1857.
[4] Ibid. 1858.
[5] Ibid. 1858.

of all these investigations are little more satisfactory than in the case of sausage-poisoning, and may be briefly summed up as follows:

The two principal kinds of sturgeon (*A. huso* and *A. sturio*) are caught in part in the Volga and its tributaries by Russian fishermen, and in part in the sea, opposite the mouths of the Emba, by the so-called "free fishermen," and by them are sold as Persian or Emba fish in the Russian fish-markets (Watogen). As these fish are often of colossal dimensions, they are immediately cut up and salted, and are then put into the fish-cellar (Wichoden [1]). The unsalted fishes, whether fresh or putrid, never set up the specific symptoms of fish-poisoning—and thus it is quite certain, as in the case of the sausage-poison, that common putrefaction is not the cause of the poison. Only the uncooked roe of the salted fish acts as a poison, and cooking perfectly deprives it of its poisonous properties.

There is nothing particularly striking about the external appearance of this poisonous food. Amongst a large quantity of non-poisonous pieces lying in the same brine, there are, as a rule, only a few, and of these again only certain portions, which are poisonous, and these are only distinguished from the harmless masses around by rather less consistence, lighter color, and a nasty taste and smell. These changes, it would appear, are now attributed to the defective salting, or salting of portions already putrid, of the inferior or Persian fish. Of the nature of the poison we know just as little as of the sausage-poison. Owsjannikoff has demonstrated that the salt-brine in which the poisonous fish has lain does not set up the specific symptoms. The outcome of all the various untenable hypotheses simply comes to this, that the fish-poison is probably due to a modified decomposition or putrescence, only developed in the salted fish, and as to whose nature, products, etc., etc., nothing certain is really known.

Any trustworthy statistics as to the frequency of this poisoning, the relative mortality, accurate geographical distribution,

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[1] Wooden boxes, sunk about two fathoms deep in the earth, in which the fish are preserved between layers of ice.

etc., such as those given of the sausage-poisoning, are rendered impossible by the vast extent of the Russian territory. Meanwhile, fish-poisoning seems no way inferior to botulismus, and commonly enough ends fatally. The two sorts of poisoning cannot, however, be considered identical, when an accurate comparison is made of the symptoms. However, they are so far similar, inasmuch as in fish-poisoning also the nervous phenomena are complicated with gastro-intestinal symptoms.

The first symptoms do not occur before an hour, and not later than five hours after the use of the poisonous fish—they consist in oppression in the epigastrium, vertigo, darkening of the face, yellow and red vision (chromatopsy), and violent burning, with a feeling of dryness, in the throat.

The sick are periodically attacked with violent pains in the region of the stomach, which generally compel them to lie on the belly and to press the abdominal walls strongly inwards. In this way the abdomen appears to be retracted, and assumes the shape of a trough. The pains gradually extend to the rectum and the loins. As a rule, vomiting is absent. On the other hand, those poisoned suffer from great precordial anxiety, tedious dyspnœal breathing, and very troublesome difficulty in swallowing, which, in the more intense cases, amounts to complete aphagia. Every attempt of the thirst-tormented patient to drink water excites the most severe cramps and a great amount of dyspnœa. The voice also becomes hoarse and toneless, and in the severer cases there is aphonia.

The nervous symptoms, which begin with vertigo, disordered vision, etc., gradually increase to a more or less perfect paralysis of the voluntary muscles, whilst the higher faculties of the brain—consciousness, etc.—are retained to the last. The faculty of sight is totally lost towards the end of life; the pupils are dilated and immovable. Ptosis is also named as a frequent symptom of this stage, at the end of which death occurs by stoppage of the breathing, whilst the heart continues to beat for some time after death.

In the slighter cases, which are not fatal, most of the above named symptoms have been observed in less intensity, but they generally vanish in a few days, without leaving behind the

slightest disorder of the general health. One special form of fish-poisoning is ushered in with croupy symptoms, according to Berkowsky.

The morbid anatomy of fish-poisoning presents absolutely nothing characteristic. As to the treatment, looking at the extreme obscurity which shrouds all the symptoms, it is manifest that it must be entirely directed to the relief of symptoms.

CHAPTER III.

POISONING BY POISONOUS CHEESE.

Like other articles of food, cheese may become the vehicle of poisons of different kinds by their accidental or intentional admixture with it. But we need not dwell on this. We have here only to deal with that form of cheese-poisoning which may be called specific, inasmuch as the poison is developed from the cheese itself.

Although it is the article of animal food which is kept the longest, and although the preparation of it gives ample scope to putrefactive changes, yet cheese very seldom gives rise to severe disorders of health; and, when compared with sausage-poisoning, the cases arising from cheese are very trifling, and, in most cases, scarcely deserve the name of poisoning. The numerous kinds of soft cheese, prepared in small families or on small farms, are generally the cause of the symptoms, while it is quite exceptional to hear of symptoms arising from the use of cheese prepared in large quantities. As regards the nature of the cheese-poison, there is just as little really known as there is about sausage- or fish-poison. All that is known is, that it is usually very old and decomposing or decayed cheese the use of which by human beings has caused the symptoms of poisoning, whilst animals have partaken freely of it, and without any harm. The author knows of a case in which a dog ate a whole plateful at

once of a poisonous cream cheese which was reserved for analysis, and not the slightest symptoms of poisoning were shown by the dog, though he was watched for many days.

Many theories have been broached as to the composition and chemical nature of the cheese-poison, which need scarcely be discussed after what has been said about sausage and fatty poisons; the more so, as most of them have been refuted, and have no practical value. It would appear that, by long keeping, albuminous animal substances, such as sausages, smoked meat, salted fish, and cheese, undergo a species of putrefactive decomposition, the products of which are poisonous to human beings; whilst ordinary decay or putrefaction does not generate any specific poison, as has been shown by the fact that some people eat, without any harm, absolutely putrid and rotten-smelling soft cheese of various kinds.

Cheese-poisoning occurs rather more frequently than elsewhere in the north part of Germany (Mecklenburg, Pomerania, Westphalia, etc.), but also in every other country, here and there, in solitary cases. In France—a country where there are, perhaps, more varieties of soft, fat (cream) cheeses than anywhere else—scarcely anything is known of cheese-poisoning. As regards the external marks of poisonous cheese, nothing definite can be said; the more so as this kind of food is at best very repulsive in taste and smell to many persons; but the taste of poisonous cheese has been said, in some cases, to be strikingly bitter and pungent.

The effects consist of well-marked gastro-intestinal symptoms: colicky pains, vomiting, diarrhœa, and disgust at all sorts of food. Amongst nervous symptoms we have vertigo, anxiety, diplopia, headaches, great weariness, and muscular weakness.

Amongst the earlier recorded cases several ended fatally, whilst in more recent times the effects have been less severe, and the cases have ended in recovery after some hours, or, at most, some days.

Of twenty cases of cheese-poisoning observed in America two ended fatally, with severe pains and collapse.[1]

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[1] *Husemann*, Toxikologie.

Husemann also relates a case in which a mother and an infant at the breast both suffered from symptoms of cheese-poisoning, so that it would appear that the poison had passed into the woman's milk.

The treatment of cheese-poisoning must be purely symptomatic.

POISONING

BY

THE HEAVY METALS AND THEIR SALTS,

INCLUDING

ARSENIC AND PHOSPHORUS.

NAUNYN.

POISONS.

General Treatises.*

Taylor, On Poisons in Relation to Medical Jurisprudence and Medicine. Phila. 1848. —*Christison*, A Treatise on Poisons. 4th edition. Edinburgh, 1845.—*Orfila*, Traité de toxicologie. 4. edit. Paris, 1843.—*Husemann, Th. u. A.*, Handbuch der Toxikologie. Berlin, 1862; mit Supplementband. Berlin, 1867.—*Schroff*, Lehrbuch der Pharmakologie. Wien, 1873.—*Van Hasselt*, Handbuch der Giftlehre übersetzt von Henkel. Braunschweig, 1862.—*Buchheim*, Lehrbuch der Arzneimittellehre. Leipzig, 1859.—*Oesterlen*, Handbuch der Heilmittellehre. Tübingen, 1856.—*Falck*, Handbuch der speciellen Pathologie von Virchow. Bd. II. 1. Abtheil. Erlangen, 1855.—*C. G. Mitscherlich*, Lehrbuch d. Arzneimittellehre. 2. Aufl. Berlin, 1847.—*Hermann*, Lehrbuch der experimentellen Toxikologie. Berlin, 1874.—*Pappenheim*, Handbuch der Sanitätspolizei. 2. Aufl. Berlin, 1870.—*Casper* (Liman), Praktisches Handbuch der gerichtlichen Medicin. 5. Aufl. Berlin, 1871.—*Kuehne*, Lehrbuch der physiologischen Chemie. Leipzig, 1868.—*Otto*, Anleitung zur Ausmittelung der Gifte. Braunschweig, 1856.

CHAPTER I.

LEAD-POISONING.

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Detection of the Compounds of Lead in the Animal Fluids and Tissues.

Sulphuretted hydrogen will not separate lead from its compounds with the albuminous substances, with which it appears to be united in the body, nor from the secretions in cases of lead-poisoning. The tissue or fluid to be examined must always be ignited until all of the organic matter is completely destroyed, or better, since some of the volatile compounds of lead may be present, be treated with hydrochloric acid and potassic chlorate. From the filtrate, the lead can be obtained in the metallic form by observing the same rules as in inorganic analysis.

Special care must be taken in every case to insure the purity of the reagents used in the investigation.

Lead-poisoning is met with in two entirely different forms.

a. Acute Lead-Poisoning.

Every compound of lead which is easily soluble in the gastric juice can, when ingested in sufficient quantity, give rise to acute poisoning. In fact, however, severe or fatal cases of acute lead-poisoning are only caused by the acetate of lead, especially the normal acetate (sugar of lead). Formerly this was most frequently administered with criminal intent, but in recent times the cases are chiefly accidental. It is well established that acute poisoning of a mild grade may be caused by the use of badly glazed or old earthen or crockery ware, or of metallic vessels soldered with impure—containing lead—solder for the preparation or preservation of acid or fatty articles of food, on account of the formation of the acetate, lactate, or fatty salts of lead. Acute

poisoning by lead has also been observed after the ingestion of articles of food colored with pigments containing lead, such as confectionery (white lead), lobsters (minium), and in children after sucking and licking playthings, visiting cards, envelopes, etc., which are covered with lead paints. The poisoning of infants by rubber nipples colored with white lead is worthy of note.

The amount of sugar of lead which is necessary to produce severe or fatal lead-poisoning appears to be quite large :—from two to three drachms and upward. This renders it improbable that poisoning of the kind last spoken of can be anything more than a mild form of the acute. It has happened that much larger doses, an ounce and more, have been taken without fatal result. Formerly doses of from fifteen to thirty grains and more were not infrequently administered by physicians daily, during a considerable period.

The symptoms in acute lead-poisoning depend upon the power to coagulate albumen, which the above-mentioned lead compounds either possess in themselves, as sugar of lead, or acquire by the action of the gastric juice, as the oxide or carbonate of lead, which become converted in the stomach into the chloride ; these symptoms, in the mild, severe, or even fatal cases, are always those of corrosive gastritis ; the milder and less severe cases manifest themselves frequently by obstinate constipation. The matters vomited are not often of a dark (bloody) color. The presence of the dark line upon the gums, which will be treated of fully under chronic poisoning, does not appear to have been positively observed in the acute form of poisoning.

The intensity of the poisoning (corrosion of the mucous membrane of the stomach) is, as in all similar cases of gastritis, largely dependent upon the fulness of the stomach.

The progress of the disease is almost always very acute ; death may take place in less than twenty-four hours ; in favorable cases recovery is complete in from twenty-four hours to a few days. It is stated (Husemann) that symptoms of chronic poisoning may come on weeks and even months after recovery from the acute form.

The *diagnosis* can only be made out with certainty by finding the acetate of lead (usually sugar of lead) in the food or the

excreta. In both of these the detection of the lead is possible without the previous destruction of the organic matter.

The *post-mortem appearances* are those of acute gastro-enteritis: the mucous membrane is covered with tough whitish coagula, as if it had been tanned, and the tissue beneath is red and softened.

Treatment.—When no antidotes are at hand, give milk and the white of eggs. If there has been no vomiting, produce it by mechanical means and emetics. The best treatment is to empty the stomach by the use of the stomach-pump.

The best antidotes are undoubtedly the alkaline sulphates—sulphates of sodium, potassium, and magnesium. When these cannot be at once obtained, phosphates, alum, or dilute sulphuric acid can be used. Vomiting and purging should always be produced, since the conversion of the lead compound into the sulphate may be imperfect, or the lead sulphate left behind in the body may give rise to chronic lead-poisoning. Otherwise the treatment is the same as for acute gastro-enteritis.

b. Chronic Lead-Poisoning.

Lead in any form, if introduced continuously for a long time into the system, acts as a poison. This is evident from the fact that even the least soluble compound, the sulphate, has this effect (Gusserow). Those preparations of lead which are soluble in the gastric juice, as the acetates, carbonate, and oxide, act most surely. All of these substances appear to act in the smallest possible doses, if introduced for a sufficiently long time. Louis Philippe's household in Claremont was poisoned after the lapse of seven months by drinking-water which contained not more than 0.0015 or even 0.0002 per cent. of lead. On the other hand, doses of from three to six grains have been given for some time, certainly for weeks, without any symptoms of poisoning having been produced.

There are many ways in which these substances may be introduced into the body. Chronic lead-poisoning is frequently produced by moderate internal use of sugar of lead, and by the

too energetic application of lead preparations in the form of cataplasms and plasters to the mucous membranes, wounds, or ulcers. Especially liable to lead-poisoning are workmen in white-lead factories (carbonate and oxide of lead), painters (white and red lead), weavers (lead weights on the looms), workers on gas- and water-pipes (lead cements), plumbers, printers (types), potters (glazing of common pottery ware and tiles), lead-, tin-, and type-founders, workmen in file manufactories (striking files on lead cushions), workers in colored paper, sewers and makers of lace (the silk and lace being treated with lead compounds or weighted with lead), brush-makers (the bristles being colored by boiling with lead preparations), and workers in enamel, especially in glass enamel.

Cases of chronic lead-poisoning have also been observed in actors and others who frequently use cosmetics containing lead, also as the result of cooking in badly glazed crockery ware (Schoenbrod), of drinking beer drawn through lead pipes, or of beer and wines from bottles (shot used in cleaning the bottles having been left); some cases have even been due to the use of snuff, which has been packed in spurious (lead-containing) tin-foil (the discovery of this method of poisoning has been wrongly attributed to M. Meyer[1]), and from sleeping on hair-mattresses (? Hitzig), the horse-hair having been dyed black by lead compounds, and poorly cleansed. One most remarkable case is that of a proof-reader, who was poisoned by reading printed proof for many years.

Very rare are cases of poisoning, due to drinking-water contaminated with lead by being drawn through lead pipe, although such cases have been observed. This rarity is explained by the fact, that almost all waters contain gypsum, which causes the formation of a coating of the insoluble sulphate of lead upon the inner surface of the pipe. The so-called soft waters, which contain but little mineral matter—such as rain and river waters, after having been kept for a long time in lead cisterns or wooden ones painted with lead paint or in badly tinned vessels—have frequently produced cases of severe lead-poisoning.

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[1] Compare *Tanquerel des Planches*, loc. cit.

With rare exceptions, severe cases of chronic lead-poisoning occur only in workers in lead, and the employments which most frequently give rise to it are those of painters, workers in white-lead factories, type-setters, lapidaries, and plumbers.

As already mentioned, the quantity of lead taken in a single case has not so much effect in producing the disease as its continued introduction; since it always happens, that even where very large amounts of lead compounds are ingested, only a very small quantity is absorbed into the blood, and it is almost immaterial whether the compound used is one which is easily or but slightly soluble. This is shown to be very probable by the fact that, in all cases of chronic lead-poisoning, the blood and internal organs contain but very small amounts of lead (0.02 per cent. in the maximum, Heubel); the elimination of the metal with the urine is certainly quite small, at least with urine which is free from albumen. In albuminous urine there appears to be a larger amount of lead. Yet Lehwald's view, that all of the heavy metals enter the urine in combination with albumen or with substances like leucin, etc., is incorrect, or at all events not proven. Lead is found in the bile and fæces (Heubel), but in too small an amount to account for the elimination of much of the metal from the body.

In the blood and all of the organs lead is found only in combination with albumen, and there can be but little doubt that it is absorbed in this form.

In cases of poisoning caused by remaining in a room, the air of which contains lead in a finely divided state, it is still undecided to what extent the absorption takes place from the mucous membrane of the air-passages. The possibility that the lead dust in the air can be applied to these passages is self-evident, but we still lack conclusive evidence that poisoning is caused in this way. There can only be a question about particles of lead suspended in the air as dust, since all of the preparations of lead are non-volatile; in the light of this fact we must judge of those cases of chronic lead-poisoning which have been reported as having been caused, for example, by sleeping once in a freshly painted room.

In all cases the conveyance of the lead into the stomach

appears to play the most important part, whether the lead preparations adhere to the hands, and are transferred from them to the food, or whether articles of food and drink are contaminated by lead dust which falls upon them. Also when lead dust in the air of rooms is the cause, the principal portion of the lead preparation probably finds its way to the stomach by the swallowing of the particles, which adhere to the mucous membrane of the mouth.

Still, it should be particularly remarked that lead dust in the air is of the greatest importance to the laborer. Bad ventilation of the work-rooms, the carrying of dust in the working-clothes to the living-rooms, or living and sleeping in the working-rooms, favors the production of poisoning in great degree. Especially bad is the habit of eating food in the work-rooms, or of drinking water which has stood in the same; also, according to all authorities, simple uncleanliness, unwashed hands before eating, and the habit, which many workmen have, of holding between their teeth or lips the paint-brush, types, or other article.

All those influences which affect the nutrition of the individual remain to be considered, such especially as the use of alcoholic drinks, which increases largely the disposition to be affected by lead. There is no doubt, however, that, apart from the variety of manifestations in single cases, one person is more easily affected by poison than another. This is shown by the fact that in some persons the first symptoms of lead-poisoning are very often followed by others, in spite of all care; but there are others who have been exposed for ten years at a time to the greatest danger of chronic lead-poisoning without showing any severe symptoms.

The greater susceptibility of women, mentioned by Tanquerel, is not proven, but children appear to be more susceptible than adults. The summer months show a greater frequency of cases (Tanquerel), due probably to external influences. The time within which symptoms appear after exposure cannot be estimated; poisoning has frequently been observed within a few weeks after the therapeutic administration of considerable doses of lead compounds (see above); in other cases years elapse before the symptoms manifest themselves with certainty.

In some cases there is no exposure to the poison at the time when the symptoms (colic, etc.) appear. Thus one case is noticed in which the symptoms of chronic poisoning appeared fourteen months after an attack of acute poisoning caused by sugar of lead solution, and another in which they appeared fourteen days after the discontinuance of the therapeutic use of lead compounds (Sandras, Pereira, van Hasselt).

It is proved beyond doubt that symptoms of lead-poisoning can appear in people who have once been affected, years after all exposure to its action has ceased. Thus, one case is recorded by Tanquerel des Planches (No. 14 Maréchal) of a painter who, annually for nine consecutive years after leaving his business, and ceasing entirely to handle lead preparations, had attacks of well-characterized lead colic and other lead troubles.

Lead-poisoning has been observed in animals—horses, cats, dogs, and others—brought on not only experimentally, but also by living in an atmosphere charged with lead dust, drinking water containing lead, etc., colic and encephalopathy being the symptoms produced.

Nothing has been established in reference to the dependence of the manner in which the affection manifests itself upon the form of preparation used, or upon any special mode of application. Recently Manouvriez has stated that, in the case of lead paralysis at least, a local influence could be shown. Yet his cases are not conclusive, and many other observers do not agree with him. In many cases, doubtless, the influence of other poisons, as copper, arsenic, etc., is brought to bear.

History.

Chronic lead-poisoning has been recognized for a very long time. We find it hinted at unquestionably in works of the old Greek authors. Arabian physicians (Avicenna) have given minute descriptions of lead colic. It also appears that the arthralgia and paralysis were known in the early ages. The most important writers of recent times are Stockhausen (1656), and Tanquerel des Planches (1830). The works of the latter still remain the standard and guide in this subject.

General Description of Chronic Lead-Poisoning.

Persons affected with chronic lead-poisoning show, sooner or later, almost without exception, signs of impaired nutrition. Even when the patient himself experiences no diminution of his strength and general health, his aspect becomes changed, and the skin assumes a peculiar yellowish hue. This color of the skin Tanquerel designates by the name of icterus saturninus; Tanquerel does not, however, use the word icterus in the sense in which it is used to-day, but states that this color has nothing whatever to do with the biliary pigments. There is rarely wanting, as a characteristic mark of the action of lead, a dark or bluish-black line at the junction of the teeth and gums, always most strongly marked upon the upper jaw. This line shows most plainly in people who have bad teeth, with deposits of tartar upon them; care should be taken not to confound with this the livid color of the gums at their junction with the teeth, which is frequently seen in such people. The black edge of this line is due to the deposition of particles of the sulphide of lead in the substance of the gum, as Tanquerel has shown; this is probably caused by the action of sulphuretted hydrogen, which is easily formed by the decomposition of food remaining upon the edge of the gum, especially if the teeth are not properly cared for, upon the particles of lead mechanically adhering to the mouth. In very rare cases this slate color spreads over the entire gum, or even over the whole mucous membrane of the mouth (Tanquerel).

The patients themselves notice, as further signs of the action of lead upon the system, a characteristic, insipid, sweetish, mildly astringent (lead) taste, at the same time a very fetid breath, and occasionally a marked slowing of the pulse (to 40 per minute, Tanquerel).

Emaciation rarely fails to appear in cases where the action of lead has lasted for years or even longer. This emaciation is more noticeable in the muscular tissue than in the panniculus adiposus. Often the progress of the disease stops here, even though the person remains subject to the action of the lead to a

greater or less degree for years continuously. In other cases symptoms of specific lead disease appear. These may be divided into four principal forms, viz.:

1. The colic.
2. The arthralgia.
3. The paralysis.
4. The encephalopathia saturnina with amaurosis saturnina.

Colic is the most frequent of these symptoms, and encephalopathy the least; the statistics of Tanquerel give as their relative frequency:

Colic	1217
Arthralgia	755
Paralysis	107
Encephalopathy	72

As a rule, colic is the first symptom by which chronic lead-poisoning manifests itself, yet sometimes one of the other symptoms appears first; in the later progress of the disease these symptoms can interchange in the freest manner; or the same one continually recurs—colic the most frequently; much more rarely, the disease always shows itself in the same person by one of the less common symptoms, paralysis or encephalopathy. The duration of the intervals between the attacks vary very much, from days to weeks or even years. It is often noticed, that when an attack of colic or arthralgia comes on, with paralysis already existing, this latter symptom becomes aggravated. Mixed forms, or the simultaneous appearance of two lead affections, are not rare. As a rule, an attack rarely results fatally; at least death is almost exclusively the result of saturnine encephalopathy, but with this symptom it is quite common.

When there has once been a pronounced attack of lead disease, the danger of a relapse is very great, unless the cause of the poisoning can be removed. The lead dyscrasia progresses with frequent repetitions of the attacks in many cases, but in some without their further appearance; an obstinate dyspepsia is developed, and following this a more and more cachectic condition of the patient; the peculiar yellowish color gradually gives way to an anæmic one, and temporary œdema, weakness of

locomotion, apathy, and moroseness show themselves, as in all similar diseases. In the highest degree of cachexia there is occasionally a well-marked tremor, never, however, to the same extent as in mercurial poisoning. In this cachectic condition the patient vegetates for years, or even tens of years, and dies sooner or later; death is usually caused by some complication. The most important complications are: phthisis, pneumonia, pleurisy, and especially nephritis—the last is relatively very frequent; gout is also not rare in lead disease.[1] Tendency to constipation exists almost during the entire course of the disease; usually this is only severe on the appearance of the paroxysms, especially at the commencement of an attack of colic.

Anatomical Characteristics.

No characteristic anatomical change in chronic lead-poisoning is known, except the degeneration and atrophy of the paralyzed muscular tissue in cases of lead paralysis. Atheromatous degeneration of the arteries has been frequently observed. Other changes which are observed after death are due to complications and not to the lead disease proper. Only a negative result has been obtained by an examination of the bodies of those who have died with lead encephalopathy. At least, the examinations of Tanquerel, who found an enlargement of the sympathetic ganglia of the neck, of Brockmann, who found induration of the same, and of Kussmaul and Meyer, who found hypertrophy and sclerosis of the connective tissue in the cœliac ganglion, are of no value at present.

General Prognosis of Chronic Lead-Poisoning.

The prognosis in reference to the special forms in which the disease manifests itself will be spoken of in connection with each. The prognosis is especially affected by the nutrition and manner of living of the individual, and account must also be

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[1] Vide *Lancereaux*, Gazette Médicale de Paris, 1871. *Garrod,* Nature and Treatment of Gout. London. 1865. etc.

taken of the peculiar susceptibility in each case. We may assume that the sooner positive symptoms of the disease appear after the commencement of exposure to the action of lead, the greater is the susceptibility; hence the danger is greater in the case of young persons, if they cannot avoid exposure to lead.

In all cases in which the symptoms have already appeared, the prognosis is bad, unless the patients can be completely removed from the influence of the poison. The prognosis depends somewhat also upon the form of the attack: encephalopathy and paralysis, or even arthralgia, indicate generally a more severe seizure.

In severe cases, the attacks are repeated, but seldom in the milder cases; and death, or complete invalidism resulting from the lead cachexia, is the unavoidable result. The prognosis is much better in those cases where the marked symptoms of lead-poisoning are wanting; in such cases the cachexia generally makes much slower progress, and it not seldom happens that the apparently severe digestive disturbances due to lead remain stationary for many years, the patient being able to work during the whole time.

In those cases in which the patient can be removed from the influence of the poison, a complete cure may be expected; yet attacks of the colic, etc., are occasionally met with weeks, months, and even years after the removal of the patient from the influence of lead. The degree of the cachexia in such cases is important in enabling us to judge of them; if it is very marked, the prognosis must be a guarded one.

Treatment of Lead-Poisoning in General.

Rapid elimination of the poison and the prevention of its further absorption only will be dealt with. A discussion of the means of treating individual symptoms, or of counteracting the existing anæmia, would be out of place here.

To facilitate the elimination of the metal, the administration of potassium iodide is to be recommended, as well as in the case of mercury (Melsens et al.). The action of this remedy is so great that, according to Michel, its habitual ingestion by those

exposed to the action of lead is a sure prophylactic against poisoning. In addition to this, recourse should be had to means which hasten tissue metamorphosis. In this way may be explained the peculiarly favorable effects of warm baths in cases of chronic poisoning by lead and other metals.

More important is the prophylactic treatment—the diminution or prevention of the introduction of lead. This is easily accomplished in cases of accidental or criminal poisoning, when it is only necessary to ascertain the nature of the disease and source of the poison, in order to stop its absorption at once. It is much more difficult where the poisoning is the consequence of a certain occupation.

First, it should be regarded as settled, that there is no certain antidote. The reputed efficacy of sulphuric acid lemonade has no foundation; this Tanquerel knew long since, and there can be no longer any doubt of its entire inefficacy, since we know that the sulphate of lead shares the poisonous properties of the other lead compounds. Still less to be relied upon are drinks containing nitric acid and sulphuretted hydrogen.

Sponges, respirators, masks, and other complicated arrangements to protect the workmen from inhaling the dust, do not succeed, since they prove too great a hindrance to them in their work.

The only effective means are hygienic. First, care should be taken to have the work-rooms sufficiently ventilated; the most dangerous parts of the work should, if possible, be done in the open air. Next in importance is absolute cleanliness on the part of the workmen. A point of great importance, and often mentioned, is to forbid them, under penalty, eating or drinking in the workshop, and not to allow them to leave the room without carefully washing their hands. It should further be absolutely insisted upon, that they change their clothing, at least their outer garments, before leaving their work. Opportunity should be given them in or near the factory to frequently take warm baths. Méhu recommends, for the purpose of thoroughly removing from the skin any particles of lead which adhere to it, that the water of the bath should contain sodium hypochlorite, which he prepares by mixing in two and a half gallons

of water thirteen ounces of chlorinated lime with sodium carbonate.

A not unimportant point, which Tanquerel has already mentioned, is that in factories in which lead compounds are used, the different parts of the work are dangerous in different degrees. Hence no one person should be employed on the same kind of labor, especially the more dangerous ones, continuously. And immediately upon the appearance of the slightest symptom of lead-poisoning, the workmen should be, for a time, removed from the more dangerous work. In an otherwise badly managed white-lead manufactory in Switzerland, in which the Dutch method is used, there has been no case of severe lead disease for many years, on account of the observance of the last two precautions.

Lead Colic (Colica Saturnina).

As already mentioned, this is the first, and by far the most frequent, form in which chronic lead-poisoning manifests itself. Not unfrequently it comes on very suddenly, without any previous symptom; in most cases, however, some warning is given. For weeks preceding the attack of colic, the patient is tormented by moderate wandering pains, which are sometimes more severe immediately after eating, and sometimes are entirely independent of meals. At the same time increased disturbance of digestion is noticed, loss of appetite, increase of the peculiar sweetish taste, which perhaps already exists as a sign of lead-poisoning, increase of constipation, and in some cases diarrhœa. With these prodroma the case can be arrested, if the proper treatment is resorted to immediately; in most cases these symptoms are followed by the outbreak of the disease, beginning with colicky pains. These vary in intensity; they may be inconsiderable, or may, on the other hand, be so severe that the patient attempts suicide. According to the severity of the attack, the patient is affected mentally in a greater or less degree, often being excited to the utmost violence. Besides the attacks of colic, which rarely last more than a few minutes (Tanquerel saw them last for hours), there are some sensations of pain which do not entirely

cease, a continued griping and cramp in the abdomen being present almost without exception.

Pressure on the abdomen never increases the pain in severe attacks, but, on the contrary, almost always gives relief; at the time of the remission it is agreeable to the patient, and very rarely increases the pain. The seat of the pain varies; generally it is in the region of the umbilicus, sometimes in the upper and sometimes in the lower part of the abdomen, and rarely in the region of the kidneys; no classification of lead colic based upon this is of any value.

In many cases the pains are accompanied by tormenting and frequent tenesmus; in others, together with or in place of tenesmus, there is strangury or retention of urine, with severe pain extending along the course of the ureters or spermatic cord to the kidneys, or to the penis. There are also shooting pains in the breasts. These pains are doubtless in part due to powerful contraction of the intestinal wall; at all events, Tanquerel succeeded in feeling very energetic contraction of the rectum, during an attack of colic, by digital examination; he also thought that he could detect a contraction of the sphincter vesicæ by the introduction of a catheter.

In addition to the colic, retraction of the abdomen and constipation are rarely wanting. The retraction of the abdomen is often very great—so great that the bodies of the vertebræ can be seen through the skin of the abdomen. The entire abdomen is generally sunken, so as to be boat-shaped, and is hard; at times the retraction is irregular. In not a few cases, however, this is entirely wanting, and in its place there is swelling of the abdomen. The same is true of constipation; notwithstanding the importance of this symptom in the diagnosis of lead colic, yet it is in many, and even severe cases, wanting, and diarrhœa occurs in its place. Nevertheless, in by far the majority of cases constipation is coincident with the pain, not only in time but also in degree, and they may last for several weeks.

Violent vomiting, or at least nausea, is also a very common occurrence. The vomiting is often preceded for a long time by ineffectual retching, and occurs generally during the

remission of the colicky pains. The vomited matters are usually tinged with bile.

In addition to the symptoms which have been already mentioned, others which appear to be constant, or at least frequent, are the peculiar pulse and the icterus. The latter, in most cases, occurs only in a mild degree—recognized by the yellow color of the sclerotic and feeble reaction to the tests for bile pigments—and is without importance; it is very rarely intense.

The peculiar pulse is certainly one of the characteristic symptoms of lead colic. It is always diminished in frequency and often to a considerable extent—to 30 beats per minute (Eulenberg); it is usually full and very hard. Its condition is considered of special value in connection with the theory of lead-poisoning. According to Tanquerel, the pulse is frequently irregular, *i. e.*, variable in frequency, but not intermittent.

Respiration is, especially during the attacks, somewhat increased in frequency without any existing disease of the lungs. Fever rarely exists, and the increase of temperature is always inconsiderable.

The appetite is always much diminished, and the urine is usually concentrated; in regard to its quantity we have no certain data; it frequently contains a small amount of albumen.

The intellect is always intact except during very severe attacks of colic.

The course of the disease, chiefly limited to the colic, is very varying. As a rule, it is more severe in the evening and night, when all of the symptoms become worse. Even after long intervals free from pain, and when the disease seems to be at an end, relapses are very frequent; they occur after the expiration of days and weeks. The duration of the disease is, as a rule, not more than a week, especially in recent cases, but it can be prolonged very much by repeated relapses, and may finally, especially in old cases and where there is a fresh exposure to the action of the poison, become chronic.

The termination of the disease following the cessation of the colic is often very sudden; then all of the other symptoms cease—retraction of the abdomen, constipation, vomiting, diminution of the pulse—and complete recovery is often surprisingly rapid.

The complications consist of the other forms of lead-poisoning, and in addition to these, some observers have noticed violent attacks of enteritis.

The prognosis is on the whole very favorable ; death in cases of lead colic is caused by the supervention of encephalopathy, rarely by lead paralysis or any accidental complication. According to Tanquerel's extensive statistics, the mortality is two per cent.

Post-mortem examination in cases of death during lead colic reveals nothing important. With the exception of the more or less limited or widespread contraction of the intestinal canal, and hypertrophy or atrophy of the intestinal wall, the autopsy gives a negative result. The appearances reported by Kussmaul and Meyer, mentioned above, were found in one case, in which the patient died after a single attack of colic with symptoms of severe enteritis.

The treatment of lead colic has always been regulated by the most varied theoretical views. Attempts have been made to render the poisonous metal innocuous by sulphuretted hydrogen and ammonium sulphide, and by baths of the alkaline sulphides ; the supposed inflammation was counteracted by antiphlogistic measures, etc. Here also we must refer to the classical work of Tanquerel, who was deeply interested in the history of this subject. In this disease, where there is no clear insight into the manner of progression, and where empiricism has not been able to establish a specific remedy, a rational treatment can only be directed to the symptoms, and the main object is to counteract the colicky pains by means of warm baths, hot fomentations on the abdomen, and narcotics internally and subcutaneously. Of the narcotics, opium has for a long time been preferred in this disease. Morphia undoubtedly answers the same purpose, and chloral taken internally has the most excellent effect, as in all spasmodic conditions of the muscles of the alimentary canal. Cathartics have been found by experience to be of great value, and we are not justified in ignoring them by the theoretical consideration that the primary spasm of the intestine is the cause of the suffering. As a rule, mild cathartics, such as senna, magnesium sulphate, and castor oil, together with narcotics, are

sufficient; in severe cases purgatives should be used—even croton oil, as recommended by Tanquerel, one drop daily in thick barley-water. Violent vomiting may be treated with ice pills, and narcotics given subcutaneously, if necessary; the other remedies required, especially the cathartics, should be given, under these circumstances, as enemata. Any existing icterus, albuminuria, etc., require no special treatment.

Too much must not be expected from drugs given to hasten the elimination of the lead from the system, for reasons which will be discussed later when speaking of theoretical points. Most can be accomplished in this respect by the use of warm baths and cathartics, and the use of potassium iodide is occasionally indicated.

Arthralgia Saturnina.

This is, according to Tanquerel, the second in frequency of the forms in which chronic lead-poisoning manifests itself. In its course there are many points of similarity with lead colic. After prodroma similar or analogous to those of colic, or even without prodroma, there appear, more or less suddenly, tearing and burning pains, located in the region of the joints or of the muscles over them. These pains exhibit violent exacerbations and remissions until they completely disappear. They are not of a true neuralgic nature, since they do not follow the course of the nerves. The existence also of the characteristic pressure points,[1] as in the so-called joint neuroses (Esmarch), is not clearly established. The exacerbations are accompanied by cramps, *i. e.*, tonic contractions of the muscles involved, which are very painful to the patient. These cramps are demonstrable by the hardening of the involved muscles and consequent position of the limb. The attacks are brought on by exercise and by cold. The pains are diminished by pressure; inflammatory appearances, such as swelling, etc., over the joints, ligaments, and tendons, are entirely wanting.

These pains occur by far most frequently in the lower ex-

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[1] See Vol. XI. of this Cyclopædia, p. 291.

tremities, especially over the knee, much less often in the upper extremities (elbow, shoulder). The muscles most frequently attacked in the extremities are the flexors (Tanquerel): in the leg, those muscles which form the calf of the leg; in the thigh, the flexors of the leg; and then the flexors of the thigh in the bend of the hip. The same is true of the upper extremities; in the body, often the long dorsal muscles are affected, especially those in the region of the loins; in the thorax, all the muscles may be affected, and the resulting affection may, in severe cases, very closely resemble angina pectoris (Tanquerel). Occasionally the muscles of the neck are involved. The smaller joints and the muscles about them are rarely affected.

A tremor of the affected muscles is often noticed. The severity of the pain is often very great, and under such circumstances its reaction upon the general condition of the patient is felt. Otherwise this symptom shows less irregularity than lead colic. Constipation and the peculiar character of the pulse are absent. There is also no fever.

Its course, as already mentioned, is not unlike that of lead colic. The pain suddenly ceases after many variations and remissions, and with the cessation of the pain the whole affection disappears, but there is the same tendency to relapse. No complications need be mentioned, except the frequent occurrence of this disease after, simultaneously with, or preceding attacks of lead colic and other lead affections.

The prognosis is, on the whole, more favorable than in lead colic, especially in regard to mortality.

Treatment.—Warm baths doubtless have the greatest effect. That sulphur baths are alone sufficient (as Tanquerel asserts) would be doubted at the present time; the number of cases upon which Tanquerel bases this statement is not sufficient. In addition to warm baths, galvanization locally and of the sympathetic should be tried.

The use of purgatives is not to be recommended; potassium iodide should be tried, since it seems to act favorably in all rheumatic affections (muscular rheumatism, etc.).

Lead Paralysis.

This is the third of the lead affections, both in frequency and in order of succession. It is observed generally after the colic or the arthralgia, or after both, but may, like all of the forms of lead disease, occur without having been preceded by any of the others. Tanquerel's compilation is interesting, showing as it does that paralysis may occur as early as on the third day after the first exposure to lead; further, that in 102 cases, 9 occurred in the course of the first month, and 14 in the course of the first two months; that 34 developed in the course of the first two years, though often this symptom did not appear until much later—thus 48 cases occurred after ten years, and some even after fourteen and twenty years. Even after fifty-two years of exposure to lead without any serious detriment lead paralysis has been observed.

In its localization lead paralysis shows an almost freakish opposition to arthralgia, which is seemingly so nearly related to it. In the latter a predilection is manifested for the lower extremities and for the flexors, while in paralysis, in the great majority of cases, at first at least, the upper extremities and the extensors are attacked. Paralysis of the extensors of the hand and fingers (especially of the extensor communis), with freedom of the supinator, is the characteristic and well-known form of lead paralysis; next, the triceps and deltoid are most frequently attacked. The same is true of the lower extremities when they are attacked, which rarely takes place until long after the paralysis of the hand and fingers, the extensors (dorsal flexors) of the foot, on the peroneal side, and those of the toes losing their power. Only in rare cases are the respiratory (intercostal, Tanquerel) or the laryngeal muscles affected. Rare, however, as cases of this form of paralysis, consequent upon lead-intoxication, are, still its relationship to the large group of lead diseases is positively established by the frequent appearance of paralysis of these muscles in animals poisoned with lead. Horses in lead-mills frequently have paralysis of the vocal-cords, rendering tracheotomy necessary. Even Tanquerel has never observed

paralysis of the muscles of the face or eye in lead disease. It is to be especially observed that the extent of the paralysis, as in the forearm, does not correspond with the distribution of a peripheral nerve.[1] The muscles affected in ordinary lead paralysis of the hand and fingers are, as a rule, those which are supplied by the radial nerve, but usually one or more of the muscles receiving fibres from this nerve remain unaffected.

In the majority of cases the paralysis affects the extremities of both sides, and often the same muscles in both extremities. There are cases, however, in which only one extremity is affected, and cases are not very rare in which the muscles paralyzed in the two extremities are different. In rare cases lead paralysis may resemble hemiplegia, on account of both the upper and lower extremity on the same side being attacked.

The characteristic appearance of lead paralysis is often obscured by the fact that it may be exceedingly limited—confined to the extensor of a single finger, for example—or by the fact that beginning in the usual manner, it may involve all of the muscles of a limb, or may even finally spread over the whole body. Very slight impairment of the function of the flexors is observable at an early stage, even when the paralysis seems to be purely of the extensors. Tanquerel, and after him others, explain this by the defective extensibility of the paralyzed muscles. Better is the explanation, that in pure extensor paralysis the position of the hands, for example, is unfavorable to the exercise of the flexors, and limits their function. Sensibility is usually unaffected in lead paralysis; more frequently there are at the commencement pains in the affected muscles or corresponding bones, and often in other muscles; rarely there is slight and very rarely complete anæsthesia of the skin, corresponding, or nearly corresponding, to the distribution of the paralysis; in individual cases there is anæsthesia of the deeper parts also. On the other hand, trophic disturbances are never absent. The extraordinarily rapid atrophy of the paralyzed muscles, often reaching a high degree in a few weeks, is, next to the localization, the most characteris-

[1] Vide *Ernst Remak*, Zur Pathogenese der Bleilähmung. Inaug.-Dissert. Berlin. 1875.

tic sign of lead paralysis. The shrinkage of the muscles attains a degree seldom seen, except in progressive muscular atrophy, and it is so much the more apparent in this disease, since the neighboring muscles preserve their normal and well-developed volume; thus the atrophy of the extensors produces a deep furrow on the outside of the forearm. By examination with electricity there appear early those signs which are seldom wanting in peripheral neuro-paralysis: speedy diminution even to complete disappearance of the reaction to the faradic (interrupted, induced) current; unchanged, temporarily increased reaction to the galvanic (constant) current; occasional appearance of greatly increased excitability to mechanical irritants; predominance of KaSZ,[1] and increase of the time occupied by the contraction wave. The observation of Erb, who found this abnormal reaction very well marked in a patient with lead paralysis in muscles in which the paralysis had not become developed, is very interesting and important. In the further course of the paralysis many deformities may arise, such as dislocation in the more movable joints, as the shoulder and phalanges, and the tumors thus formed—upon the back of the hand, for example—can very easily be mistaken for gouty swellings; as mentioned above, however, true gouty swellings occur as a complication. Often there is tremor of the paralyzed muscles (Tanquerel), especially at the time of the appearance and disappearance of the paralysis. Tremor is also frequently observed in the facial muscles, which are never affected with lead paralysis.

The onset of the paralysis usually follows certain prodroma, such as sensations of pain and dulness in the affected limbs; it comes on quite gradually, though sometimes suddenly, after an attack of colic or encephalopathy, and simultaneously with or soon after the cessation of these. In rare cases it comes on suddenly and without any prodroma. Once started, it may extend gradually and irresistibly.

The progress of the paralysis is very varied. It may disappear spontaneously, or under treatment, in a few days or weeks; or it may become stationary at any stage and last for years.

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[1] See Vol. XI. of this Cyclopædia, p. 273.

in cases where it remains, it becomes worse with the onset of any new form of lead disease. Convalescence, almost without exception, is gradual, yet, considering the extent of the paralysis and atrophy, comparatively rapid, the atrophied muscles being replaced by new tissue. Relapses in the same muscles are not rare.

The prognosis depends upon the length of time during which the paralysis has lasted, and upon the extent of the atrophy; the greater these, the more unfavorable is the prognosis; the more extensive the paralysis, the worse the prognosis; it is more unfavorable in the relapse than in the first attack; it is doubtful, where there is only considerable atrophy, and it is not absolutely bad where the atrophy is not complete. Tanquerel observed a fatal result follow, in two cases of paralysis of the intercostal muscles, by asphyxia.

In addition, we would mention progressive muscular atrophy as having been frequently observed in patients suffering with lead disease.

The *pathological changes* are found in the muscles and peripheral nerves. Examination of the central nervous system has always given negative results. The most important change is that observed by Westphal, who found in one case of lead paralysis, which developed gradually during two years, an abundant new formation of nerve-fibres in the radial nerve, which he rightly considered to be due to previous degeneration; this was confirmed by an earlier observation of Lancereaux.

Several authors, and among them Bernhardt, found, in examining muscles atrophied by lead paralysis, that they were shrunken and very granular, and between the fibres he observed an abundant formation of connective tissue poor in nuclei—in part probably the empty sheaths of fibres, the contents of which had disappeared.

Treatment.—Besides the means employed in lead disease generally—tonics, warm baths, potassium iodide—electricity in its different forms, such as local faradization and galvanization, is the special treatment for lead paralysis, and very beneficial results are doubtless obtained by it. The use of strychnia in this disease, as in others, has been nearly forgotten. The powerful effect which this substance has been shown to have

upon the excitability of the nervous system, and the wonderful results which have been obtained by its use in other fields, should warrant its more extensive employment in this also. The statement which Tanquerel makes concerning the action of this drug in lead-poisoning is of great interest, and his assertion that it gives good results is quite credible. Tanquerel gave this drug internally and by the endermic method in slightly toxic doses ; in most cases he gave it until slight tetanic spasms were produced. The enormous doses which he speaks of—up to nearly two grains, usually from one-sixth to one-half grain—were probably borne, as he himself thought, owing to impurity of the preparation used. The use of this drug is indicated in lead-poisoning where the patient for any reason cannot bear the application of electricity, or where the latter does not soon give visible results. It may be given by the mouth, or, if feasible, locally by subcutaneous injection. It should be remembered that relatively large doses are required to produce good effects, and also that the susceptibility of different individuals to the action of the drug varies greatly; that occasionally this drug appears to have a cumulative action; and further, it should be remembered, when about to increase the dose, that therapeutic and very toxic doses lie very closely together.

Brief mention must here be made of the anæsthesia, not including amaurosis, which will be treated of later under the head of encephalopathy.

Anæsthesia, properly speaking, is rare in lead-poisoning; Tanquerel observed it in eleven cases. Usually there is anæsthesia of the skin only, rarely of the skin and deeper tissues. It has no definite relation to the muscular paralysis; it may appear with paralysis and also with colic and arthralgia. There may be both arthralgia and anæsthesia of the skin in the same locality.

On the whole, in localization and in its course it is very varying and, as it were, freakish. The attack in one place disappears to-day only to appear in another in a few days ; according to Tanquerel, its distribution is rarely confined to any particular

nerve-track. It rarely lasts longer than fourteen days. The prognosis is therefore favorable, and the treatment unimportant —warm baths and, if it should be at all permanent, electricity and strychnia.

Encephalopathia Saturnina.

Under the name of encephalopathia saturnina are comprised all of those conditions which, depending doubtless upon an affection of the brain, are developed under the influence of lead. By far the most important of these, not only in regard to its frequency, but also in regard to its prognostic importance, is the eclampsia saturnina. A description of all of its different forms as separate varieties, as Tanquerel preferred to do, is too discursive; this has always conduced to the formation of mistaken ideas—which are inclined to identify encephalopathy, or only the eclampsia saturnina, with uræmia—so that too much attention has been bestowed upon a single form, the eclamptic, while the closely allied but symptomatically very different conditions of simple coma and other brain symptoms have been scarcely noticed.

Encephalopathia saturnina is in every respect the most severe of the forms in which chronic lead-poisoning manifests itself; hence it is found almost exclusively among laborers whose work favors a copious absorption of the poison, and in them it occurs in a proportionally large number, and often surprisingly early; of 72 cases collected by Tanquerel, it was developed in 1 in eight days; in 10 in the course of the first month; and in 44 in the course of the first nine months; on the other hand, in only 28 cases was it developed in from one to fifty-two years after the individuals had begun to work in lead.

In animals it is very frequent, and in dogs, after experimental poisoning, it is almost always the symptom which last appears.

In lead-workers encephalopathy may come on very suddenly after one of the other lead affections, or without the precedence of such, or beginning with the prodroma usual to the disease. The most important of these are violent headache and amaurosis saturnina. Less certain symptoms are stupor and apathy or excite-

ment. The true encephalopathy develops with a more or less gradual or sudden increase of sensory disturbances, and the appearance of general or partial convulsions.

The symptoms, as already mentioned, are not the same in all cases: sometimes there is simple maniacal excitement with tendency to violence, sometimes melancholia with corresponding hallucinations; in other cases convulsive attacks appear quite early. Sometimes, but on the whole rarely, the convulsions are more partial, whilst at the same time the unconsciousness is more or less completely wanting; in most cases the appearance of acute eclamptic attacks gives the characteristic stamp to the picture; eclampsia saturnina is the most common and the principal symptom of encephalopathia.

The eclamptic attack comes on very suddenly or after the above prodroma; the attack does not at once reach its greatest intensity in the severity of the convulsion and duration of the coma, but the more severe attack comes on soon after the first mild one has passed off, and the patient has awakened from a short period of unconsciousness. After this one the coma is of longer duration, and after a while, in most cases, it does not cease at all, and the most violent epileptiform attacks follow one another in rapid succession.

According to Tanquerel eclampsia saturnina is never preceded by an aura.

Between the attacks there is frequently uneasiness and delirium, instead of coma.

Thus the case may last for several days. Where the attacks are very frequent, death usually takes place rapidly; in mild cases the attacks are less frequent, and in the interval consciousness, at first temporary and incomplete, gradually becomes fully established, or the patient may awake from a very severe attack like an epileptic from a paroxysm, and thus complete recovery ensue, which, however, not unfrequently, soon gives way to a relapse.

Amaurosis is the most important of the symptoms accompanying encephalopathy; it may, as Tanquerel says, come on before, with, or after the attack of encephalopathy, often suddenly, but in some cases gradually, sometimes also quite inde-

pendently of the encephalopathy. The appearances are, according to ophthalmologists: normal fundus oculi, normal boundaries of the field of vision, and central scotoma.

Albuminuria is not rare in cases of encephalopathy; its importance is twofold, and not always easy to determine, since albuminuria may come on as a result of the convulsions, as in severe epileptic paroxysms, and in a majority of cases it does not depend upon true nephritis. Chronic nephritis is, however, quite frequently observed in lead-poisoning. This symptom may, therefore, in many cases, add to the difficulty of a diagnosis.

Post-mortem examinations in cases of lead encephalopathy have been quite numerous, but have, up to the present time, given entirely negative results.

The *prognosis* is always unfavorable; the worst form is the eclampsia, and in it the prognosis depends upon the severity, and above all, upon the frequency of the attacks. Tanquerel, who, it appears, observed a relatively small mortality, had 16 fatal cases out of 72 of the disease; other authors give a much higher death-rate.

Treatment is entirely without avail, and the expectant treatment has, according to Tanquerel, the best success.

Theory of the Action of Lead and of Lead-Poisoning.

The theory of lead-poisoning has, both in former times and recently, been the subject of much speculation and experiment, but it has as yet been absolutely impossible to give a satisfactory explanation of the nature of the disease, based upon facts, and taking into consideration only those symptoms most frequently observed. And the value of the important work of Heubel consists chiefly in showing the insufficient foundation of certain attempted explanations, which had unjustly acquired general approval.

The view, which has recently gained some notoriety, is this: that the preparations of lead act chiefly upon the muscular fibre, especially the unstriped. When, by the gradual introduction of

the preparation, the blood becomes, as it were, saturated with lead, then the substance extends its action from the blood to the unstriped muscular tissue of the smaller arteries in the intestine and bladder. The contraction of the smaller vessels leads, on the one hand, to an increase of the blood-pressure. As a proof of this is adduced the abnormally hard pulse observed during the attacks of colic (and, according to Traube, at other times). On the other hand, it leads to anæmia, and thereby to the many disturbances of function and nutrition of the organs. In this way is explained the general cachexia, and finally, by anæmia of the brain (Rosenstein), the eclampsia saturnina. The muscular paralysis can be explained by the disturbance of nutrition in the muscular tissue, which is partly the result of the contracted condition of the smaller vessels (arterial anæmia), and partly due to the direct action of the lead upon the striped muscular fibre. The last assumption was based upon the misinterpreted experiments of Gusserow, who found a larger amount of lead in the muscular tissue of animals than in the other organs. An explanation of the fact that the lead acted upon some muscles and not upon others was attempted by supposing that possibly some existing peculiarities in the supply of blood-vessels to the affected muscles might favor this (Hitzig). The assumed action of the lead upon the unstriped muscular tissue of the intestines and bladder served to explain in a quite satisfactory manner the appearance of the colic.

The paroxysmal character of the more violent symptoms of lead disease, in spite of the gradual, long-continued introduction of lead, is explained by considering that, in consequence of the occasional diminution in the elimination of the lead (especially by a diminished secretion of urine), an accumulation of the poison in the body takes place.

The conclusions of Heubel, which are based upon numerous experiments, and which contradict the above views in almost every particular, must be accepted, and the above theory must be dropped, partly because lacking sufficient foundation, and partly because contradicting the facts.

Among the tolerably well-established facts which assist in explaining the nature of the action of lead and lead-poisoning,

and some of the symptoms of this disease, may be mentioned the following:

Lead exists in the blood and all of the organs, as has been already mentioned, in chemical combination with albumen. This is shown by the fact that it cannot be detected by chemical tests without the previous destruction of the organic substances. Hence it is not allowable to ascribe to the lead circulating or remaining in the system that astringent action which lead compounds, especially the acetate, possess.

The amount of lead which accumulates in the organs in chronic lead-poisoning is very small, as is also the amount which is eliminated with the urine. Hence it is little probable that the sudden manifestations of lead-poisoning—colic, for example—are due to the relatively diminished elimination of the lead. On the other hand, it must be acknowledged that nothing definite is yet known concerning the separation of lead with the urine in chronic lead-poisoning. The same is true with reference to the amount of lead which is eliminated with the bile, and consequently the importance of the biliary secretion in connection with this question is not yet established. It is also maintained by many that the lead is separated by the skin. This is not established, although but little can be said against such a view from a theoretical standpoint. In all of those cases in which a blackening of the skin, caused by sulphur-baths, is reported, it is not proved that this may not have been produced by minute particles of the lead compound in the form of dust, which had been deposited upon and in the epidermis.

The amount of lead which is accumulated in the different organs appears, according to all authorities, and especially from Heubel's latest investigations (reckoned of course in per cent.), to vary very greatly. Heubel found in four experiments upon dogs, poisoned by the administration of the acetate of lead for several weeks, by far the largest amount in the bones, about 0.025 per cent., the next largest amount in the kidneys, 0.012–0.02 per cent., and liver, 0.01–0.016 per cent., next in the spine, 0.006–0.01 per cent., and next in the brain, 0.004–0.005 per cent.; still less was found in the muscles (0.002–0.003 per cent.); in the intestines, after complete separation of their contents, from mere traces to

0.002 per cent. was found, and almost always only traces could be detected in the lungs and blood. Hermann rightly remarked that this order of the organs, in respect to the amount of lead which they contain, would be very different if they were considered in reference to the proportion of lead to the inorganic residue (after ignition) instead of to the total weight of the fresh tissue; in this case the bones at least would stand much lower in the list.

It must be acknowledged at the outset that this knowledge which is gained by experiments upon animals poisoned in a relatively short time, and by relatively large doses, cannot, without some allowances, be applied to the much more chronic condition of poisoning in man; the animals have, however, shown the characteristic symptoms of lead-poisoning. So far, then, as Heubel's results have any value in regard to the theory of chronic lead-poisoning, they show that the known, so to speak, localization of lead-poisoning in the intestines and muscles is not caused by the deposition of the lead directly in these organs.

Nothing further is known which can enlighten us as to the constant changes in the organs caused by lead. Of chemical results we have only the interesting one of Heubel's, that in the lead cachexia the amount of water in the organs is increased—a peculiarity which this cachexia possesses in common with others. That the results of anatomical investigations are negative has been already mentioned. It is worthy of notice that there is no hypertrophy of the heart, especially of the left ventricle, which is an argument against the assumption of those who assert that there is, as a result of lead-poisoning, a permanent contraction of the smaller vessels, and consequently an increase of blood-pressure in the arteries. Those who consider the full and distended pulse as a symptom, not of chronic lead-poisoning generally, but only of the lead colic, are, therefore, probably correct (Tanquerel).

Of the single manifestations of lead disease, lead colic is doubtless to be looked upon as a neurosis of the intestinal plexus, but it is impossible to determine whether it is due to central or peripheral causes; yet Hermann certainly goes too far, when he infers that the nature of the affection is peripheral on account of the diminution of the pain upon pressure, since this phenomenon

is also frequently observed in neuralgias which have a central origin. Whether the pain is due to violent peristaltic action, which is interfered with by the presence of hardened fæces, as Traube thinks, it is impossible to say; at all events, this is partly the cause, yet it must be remembered that the most violent peristaltic contractions in cases of obstinate constipation and obstruction are not attended with such severe pain as lead colic. Eulenberg's definition of lead colic should rather be adopted, viz., a mixed neurosis of the iliac and cœliac plexuses.

The most important general manifestations which accompany lead colic are not difficult of explanation; the peculiar hardness of the pulse, with the diminution in frequency, is to be considered as a reflex phenomenon caused by irritation of the sensory fibres of the splanchnic.

The arthralgia cannot be explained. There is no doubt that not only muscular contractions, but also direct disturbances of sensibility contribute to it. The nature of lead paralysis, in spite of the numerous and interesting investigations in regard to it, is also not yet explained; most probably it is a disease of the nervous system, and not primarily one of the muscles; at all events, nothing favors the theory of primary disease of the muscular tissue, while facts, such as the occasional very sudden appearance of the paralysis, oppose it. Moreover, Westphal's case shows that regeneration after previous degeneration of the nerve-tissue may take place in this disease. Much more difficult of solution is the question, whether the disturbances in the nervous system are of central or peripheral origin. Authors generally incline to the opinion that their origin is peripheral. Yet it is clear that the phenomenon, the observation of which in paralyzed muscles has mainly given rise to this opinion, can contribute nothing to the solution of this question—I mean the so-called reaction of degeneration.[1] Although at one time neuropathologists inclined to view it as undoubted proof of the peripheral origin of the paralysis, yet we know to-day, especially from Erb, that this reaction is not infrequent in paralysis having a central (spinal) origin. The same is true of atrophy of the muscles, which develops so

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[1] See Vol. XI. of this Cyclopædia, p. 426.

rapidly in lead paralysis; in this respect, also, observations multiply daily, which prove that it is a very common thing to see a rapid development of atrophy of the paralyzed muscles in diseases which certainly have a central, and especially a spinal origin.

We mean that in view of these facts the degeneration and regeneration of the peripheral nerves observed in lead paralysis (Westphal's case) does not exclude the supposition of a central affection. On the other hand, it cannot be denied that many things favor the supposition of such central (spinal) affection, such as the frequent symmetry of the disease and the localization of the paralysis, chiefly noticeable at the beginning, in groups of muscles more closely related functionally than by their dependence upon one and the same periphereal nerve-trunk.

There is no doubt that we do have to deal with functional disturbances of the nervous system having a central origin in encephalopathia saturnina in its different forms. And it is yet too soon to form any more acceptable theories concerning the mechanism or chemistry of these disturbances. To say that anæmia of the brain is the cause of them is no explanation; since there is neither evidence of any special brain anæmia, nor do we see anæmia of the brain, when due to other causes, act in the same manner. The most important form of encephalopathy, the eclampsia saturnina, may, in some cases in which nephritis exists, as it not rarely does in lead-poisoning, be explained as due to uræmia; but there is no doubt that in the majority of cases of lead eclampsia this explanation will not answer. In every respect the aspect of encephalopathia saturnina has much in common with chronic alcoholic intoxication, to which the name of encephalopathia alcoholica might well be given. In this disease also we have numerous interchanges of psychoses of different kinds, with eclamptic conditions and even genuine epilepsy. It should be added, also, that amaurosis of precisely the same nature occurs in both of these forms of chronic poisoning. The analogy to which we refer here is not altogether without value for the understanding of the nature of encephalopathia saturnina. Altogether too much stress has been laid upon the sup-

position that all of these symptoms of chronic lead-poisoning depend directly upon the lead which is taken into the system and deposited in the organs. In chronic alcoholism it has been an accepted view for a long time, that an abnormal nutrition of the whole system is developed in consequence of the long-continued circulation of the foreign poisonous material in the body. The functional disturbances, which finally ensue as a result of the poisoning, stand, therefore, only in very indirect relation to the poison. But why the nutrition of the central nervous system suffers in such a way that these disturbances of its function develop, is thus far an enigma. The relation of lead encephalopathy to the poison absorbed should be looked at in a similar manner; and we do not think that anything has been done toward explaining the disease by detecting the presence of lead in the nervous centres.

CHAPTER II.

COPPER-POISONING.

Oppolzer (Schnitzler), Deutsche Klinik. 1859.—*Falck*, Ibidem.—*Lieberkuehn*, Poggendorf's Annalen. Bd. 86.—*Bergeret* et *Mayençon*, Archives de l'Anatomie et de Physiologie. 1874.

In the organs and secretions of the human body copper always exists in combination with albumen, and can only be detected after destruction of the organic matter. On account of the relatively frequent necessity of examining for the presence of copper compounds in articles of food, etc., its easy detection in such cases is of interest. It is sufficient to acidulate the substance in question, such as food supposed to contain copper, with acetic, hydrochloric, or sulphuric acid, and introduce a polished steel needle, when the copper, even when only a minute amount is present, is deposited upon the needle, and may be easily recognized, since it dissolves in a little dilute ammonia with a blue color. Instead of acidulating the suspected substance, the needle may be moistened with acetic or dilute hydrochloric or sulphuric acid.

Metallic copper itself is but slightly poisonous, since it is attacked with difficulty by the gastric juice. So far as known, there exists but one well-authenticated case of poisoning by it (copper coin). The oxide of copper, the carbonate (Brunswick green), the sulphate (blue vitriol), the basic acetate (verdigris), the chloride of copper, and the salts of copper with the fatty acids are poisonous.

Acute Copper-Poisoning.

Among the sources of copper-poisoning the principal are the formation of the fatty salts or acetate, etc., by boiling or preserving food in copper vessels which have not been tinned, or which have been badly tinned. Numerous cases of poisoning have been caused in this manner. In the Vienna General Hospital there were 130 cases of poisoning caused in this way, 9 of which were fatal. This is, however, not the only way in which a dangerous amount of copper may get into food: many fruits, in order to impart to them a beautiful green color, are boiled after the addition of a small amount of some copper compound. Confectionery may be colored by covering with some copper pigment. Oysters in beds in or near copper deposits contain occasionally a considerable amount of copper.

Crabs, pickles, and tea may be colored with copper. Eating bread to which sulphate of copper has been added, and the use of spoons made of an alloy containing a large amount of copper have caused acute poisoning.

It should be especially mentioned that all of these poisonings may become dangerous to life, even when the amount of copper is not large enough to be clearly perceived by the taste.

The inhalation of the dust, which resulted from pressing the gilt letters upon the covers and backs of books in bookbinderies, has given rise to one case of acute poisoning.

Cases have been observed where the poisoning was caused by taking Radermacher's oxide of copper and, at the same time, eating acid fruits, but more frequently by the careless use of the sulphate.

The sulphate and acetate are used exclusively for criminal

and suicidal purposes; but the extremely disagreeable taste of these preparations acts as a check to their use for the former purpose.

There is much disagreement in regard to the amount which is a dangerous or fatal dose. According to some, doses not equal in amount to the maximum dose of the sulphate of copper of the German pharmacopœia (less than fifteen grains) have proved dangerous. In other cases much larger doses, up to nearly an ounce, have been taken without injury. The dose of the acetate appears to be the same as that of the sulphate.

The symptoms of acute copper-poisoning are in most cases those of a severe gastro-enteritis; the existence of great tenesmus and pains in the large intestine are noted as peculiar symptoms in many cases.

In comparatively many cases the nervous centres sympathize in a very marked degree, as shown by the violent delirium, etc. Convulsions are also not unfrequently observed; these symptoms are, however, noticed chiefly in those cases of copper-poisoning caused by food, etc., in which the diagnosis is often not perfectly clear.

Many authors mention the comparative frequency of icterus. It appears that Christison's authority alone shelters this statement. One case of acute copper-poisoning with icterus is mentioned by Orfila.

The result is favorable in by far the majority of cases. Fatal cases generally run a very acute course. It is not certain that chronic poisoning may result from an attack of acute. Yet it is thought (? Schnitzler—Oppolzer, v. Hasselt) that a scorbutic condition may result from a protracted case of acute poisoning.

The post-mortem appearances consist of very intense inflammation of the mucous membrane of the stomach; not rarely this change extends downwards into the duodenum and upper part of the small intestine. In cases of poisoning by the sulphate of copper or verdigris the blue or green color of the coating formed upon the mucous membranes is quite characteristic; in the latter case, if it be moistened with ammonia, a deep blue color is formed; the same is true of the contents of the stomach and intestines. The bodies of those who have been poisoned with

copper compounds have in a few instances been found in a mummified condition.

Treatment.—The most useful antidotes are albumen and calcined magnesia. Sugar is much recommended. So far as the theoretical merits of this remedy are concerned, only those varieties which easily act as reducing agents (grape-sugar, honey), and not cane-sugar, can be of value; but even the success of these varieties is not sufficiently established theoretically or empirically. Formerly there were recommended as antidotes, without, so far as known, having ever been tested practically, sulphide of iron, iron filings, silver filings, etc., and also the ferrocyanide of potassium.

Chronic Copper-Poisoning.

The existence of chronic copper-poisoning cannot be doubted, although in the description of it given by authors there is much that is not well established. In the first place, there is an important obstacle to the observation of pure cases of poisoning, namely, that in almost all cases of chronic copper-poisoning other metals, such as zinc, tin, lead, and others, play a part.

One fact, which testifies against any powerful poisonous action of the metal, is that the majority of workers in copper and its compounds remain perfectly healthy.

Cases of chronic copper-poisoning are reported among coppersmiths, copper-smelters, brass-workers, workers in bronze, etc.; and they have certainly been observed as a result of the continued eating of food rendered poisonous by being prepared in copper utensils. The more certain symptoms of chronic copper-poisoning are a more or less severe chronic gastric and intestinal catarrh and colic, which may be distinguished from lead colic by the fact that there is scarcely ever retraction of the abdomen, and rarely constipation, but, on the contrary, there is usually diarrhœa. Moreover, according to Oppolzer, the patient with copper-poisoning does not perceive the sweetish astringent taste peculiar to lead-poisoning, but the taste is the same as that produced by an old copper coin upon the tongue.

The presence of a line at the junction of the teeth and gums, similar to that observed in lead-poisoning, is frequently mentioned. According to some this is exactly the same as the lead-line, according to others it is purple-red in color, while, according to others, the appearance of such a red line is due to the strong contrast between the red color of the gum, especially marked at the edge of the teeth, and the greenish deposit which colors the teeth even to the gum.

Frequently there is a peculiar reddish or greenish coloration of the hair and of the skin, which is probably due to the deposition of small particles of copper, or of the fatty salts of copper.

There are no very marked disturbances of nutrition in copper-poisoning, except in those cases in which there is a gastro-intestinal catarrh. Mention is frequently made of the existence of special functional disturbances of the liver, yet I have never been able to satisfy myself of the correctness of these assertions.

Only one well-authenticated case of copper paralysis is known to me (Oppolzer). In this case the paralysis affected the right upper extremity, and was very similar to lead paralysis.

Post-mortem examinations show nothing characteristic ; mention is made of a green coloration of the soft tissues and bones, but that this is due to the presence of copper is not surely established.

Treatment.

The treatment of chronic copper-poisoning is the same as that of chronic poisoning by the other heavy metals ; no antidote is known.

Theoretical and Experimental Considerations.

The sulphate of copper gives with albumen a precipitate, which is, according to Lieberkuehn, an albuminate of copper, and contains 4.6 per cent. of copper. Therefore, the salts of copper should be absorbed in this form. The different organs of the human body frequently contain traces of copper, as has been shown, especially by Orfila, in the liver ; this amount of copper

is, however, very small. Orfila, for instance, was obliged to take several livers together for analysis, in order to be able to demonstrate to the Academy the presence of copper in them. Copper has not been detected with certainty in normal urine. Pathologically, copper is found to the largest extent in the liver, and is eliminated with the bile. It has been found in many cases in the kidneys. According to Bergeret and Mayençon, after the administration of small doses of copper compounds, it appears in the urine even without the latter containing any albumen.

Solutions of the sulphate injected into the veins act as an emetic.

In regard to its action as a drug little has been determined experimentally. Falck and others found that it exerted a powerful action upon the heart, producing death by paralysis of this organ, and in addition it produced paralysis of the muscles generally.

CHAPTER III.

ZINC- AND CADMIUM-POISONING.

Meyhuyzen, Archiv der gesammten Physiologie. Bd. VII.—*Michaelis*, Archiv für physiologische Heilkunde. Jahrgang X.—*Honssell*, Klin. Wochenschrift, 1866. —*Marmé*, Henle und Pfeuffer's Zeitschrift. Bd. 29.

Zinc is detected in the organs and secretions after destruction of the organic matter. In using potassic chlorate and hydrochloric acid the operation should be conducted over a water-bath, since the chloride of zinc is somewhat volatile. In incinerating the organs, sulphuric acid should be added in slight excess in order to prevent the formation of the likewise volatile metallic zinc (Michaelis). After destroying the organic matter, and precipitating with sulphuretted hydrogen, Michaelis recommends fusing the white precipitate with cobalt; a beautiful green color indicates the slightest trace of zinc.

Of the compounds of zinc, the sulphate and the chloride are the principal ones to be considered; at least these are the only ones which are known to have given rise to acute poisoning. As

a source of chronic poisoning, is to be especially mentioned the oxide of zinc, which is easily soluble in the gastric juice (hydrochloric or lactic acid) ; even metallic zinc is so easily attacked by weak acids, such as those in fruits and the fatty acids, that it may readily become the source of chronic poisoning, as when food is cooked or preserved in zinc utensils or those which have a zinc coating. Rain-water collected from zinc roofs always contains, according to Pettenkofer, a considerable quantity of zinc. The carbonate of zinc was formerly much used in the treatment of nervous diseases, and in this way has frequently caused chronic poisoning ; which has also been met with in manufactories of zinc white. The chloride and sulphate of zinc have been used with criminal intent, but more frequently accidentally. In one case death was caused by the external application of chloride of zinc paste as an escharotic.

Acute Zinc-Poisoning.

The amount of any of the zinc compounds necessary to produce acute poisoning is difficult to determine. From fifteen grains to a drachm of the sulphate of zinc is occasionally used therapeutically as an emetic. Fatal results only followed after taking an ounce or more. The chloride of zinc is the most powerful, and is, as is well known, a genuine escharotic, while the sulphate is classified among the non-corrosive but irritant poisons. Poisoning by this substance is not very rare, especially in England, and is almost always fatal.

The very strong metallic taste is said to be peculiar to acute zinc-poisoning. As would be expected, the symptoms of gastroenteritis are present to a greater degree in poisoning by the chloride of zinc. In these cases the symptoms of corrosion of the upper portion of the alimentary canal are strongly marked : bloody vomiting, visible corrosion of the lips and mucous membrane of the mouth, etc. On the whole, the more intense forms of zinc-poisoning are very similar to those of tartar-emetic poisoning, and both frequently and in an unexpected manner terminate favorably. In most cases recovery takes place quickly in

the course of two or three weeks at the longest, while an unfavorable termination may take place later, occasionally with nervous symptoms which are little characteristic ; in cases of poisoning by the chloride of zinc there is frequently observed, three or four weeks after the occurrence of the poisoning, a recurrence of the gastric symptoms, even after apparently complete recovery. This is not rarely noticed after poisoning by the powerful corrosives, and is probably due to the development of large ulcers or cicatrices upon the mucous membrane of the stomach. In one case of severe chloride of zinc poisoning, which terminated in recovery, Honssell observed during several days great albuminuria and hæmaturia.

Post-mortem Appearances.

In poisoning by the sulphate of zinc, the appearances peculiar to a corrosive action are wanting completely, and there is only seen here and there moderate inflammation of the mucous membrane, which is covered with a tough white mucus. In chloride of zinc poisoning the appearances of corrosion are very marked, and often ulceration and cicatrization of the mucous membrane of the stomach are seen, and in one case there has been observed considerable contraction of the pylorus. Extensive gangrene of the wall of the stomach and œsophagus has been noticed.

Treatment.

Albumen and milk should be given, and the expulsion of the albuminate of zinc formed should be hastened; large amounts of the carbonates and phosphates are the best antidotes. Decoctions containing tannic acid are recommended in order to form the slightly soluble tannate. The ordinary treatment of simple or ulcerative gastritis must be resorted to if necessary.

Chronic Zinc-Poisoning.

As already mentioned there are numerous cases recorded of chronic poisoning in zinc mines and manufactories of zinc preparations caused by the vapor and dust. Most of these are not certainly cases of pure zinc-poisoning, since other metals which are impurities in zinc frequently take part. In this manner, copper, lead, and even arsenic, may exert their effects. The possibility of chronic zinc-poisoning, however, cannot, according to Michaelis' investigations, be doubted, and its existence has been proved by the occurrence of cases caused in former times by the therapeutic administration of zinc compounds.

In these cases the long-continued use of relatively large doses in epilepsy, etc., has led to symptoms of chronic gastro-intestinal catarrh with marasmus which gradually reaches a high grade.

The description of those cases of chronic zinc-poisoning which occur in factories shows them to be very similar to those of chronic lead-poisoning: dyspepsia, emaciation, colics, with constipation, but most generally with diarrhœa, muscular pains and contractures were present; at the same time it is very difficult to exclude the simultaneous influence of lead.

Certainly the poisonous influence of the dust and vapor is very slight, since cases of poisoning are quite rare, although the dust is developed in enormous quantities.

Treatment of Chronic Zinc-Poisoning.

Cases of chronic zinc-poisoning are described as easily curable even when far advanced. Sulphur baths are recommended as the most effective means. No use has thus far been made of potassium iodide. Melsens' experiments speak very favorably of its beneficial effects.

Theoretical and Experimental Considerations.

The sulphate of zinc, and apparently the other zinc salts also, forms with solutions of albumen an albuminate of zinc,

which contains, according to Lieberkuehn, only traces of sulphuric acid and a tolerably constant proportion of the oxide of zinc (4.7 per cent.). In this form the salts of zinc are probably absorbed into the blood and exercise their power, since vomiting takes place as readily after the ingestion of the albuminate as of the other salts. Vomiting and the other symptoms of the action of zinc are observed also after the subcutaneous injection and injection into the veins. In the organs zinc can only be detected in combination with albumen. Michaelis found it in largest amount in the bones and in the liver, also in the brain and in the muscular tissue. The bile seems to contain a relatively large amount. After taking moderately large amounts the zinc can only be detected in the urine after four or five days.

The elimination with the bile increases, according to Michaelis, with the duration of the poisoning, but is not sufficient to separate the metal quickly from the body. Orfila found zinc in the liver sixty days and more after the discontinuance of its use. Experiments as to the action of zinc have shown that chronic gastritis and even ulceration follows the ingestion of the oxide of zinc. After using it for several weeks there occur general convulsions, accompanied by peculiar twitching of the limbs.

Meyhuyzen found, as the action of the acetate of zinc given subcutaneously in doses of from one-thirteenth to one-sixth of a grain, rapid (complete in thirty minutes) destruction of reflex excitability.

The action of sulphate of cadmium and other cadmium salts appears to be the same as that of the zinc compounds, only, on the whole, more energetic. Severe cases of poisoning are said to have been caused merely by the inhalation of the dust. Half a grain of the sulphate of cadmium is said to produce vomiting easily.

CHAPTER IV.

SILVER-POISONING.

Bael, Gazette médicale. 1865.—*Frommann*, Virchow's Archiv. Bd. 17.—*Riemer*, Arch. für Heilkunde. Bd. 16.—*Lionville*, Gazette médicale de Paris. 1868.—*Bogoslowski*, Virchow's Archiv. Bd. 46.—*Scattergood*, British Medical Journal, 1871.—*Duguet*, Gazette médicale de Paris. 1874.—*Rouget*, Arch. de Physiologie norm. et pathol.

The detection of silver in the tissues and secretions is accomplished after the destruction of the organic matter. When present in the organs in large amount it can usually be detected microscopically; in such cases it is deposited apparently as a metal, in the form of fine dark granules.

Practically, the nitrate of silver only need be considered. Cases of poisoning by it may be acute or chronic.

1. *Acute poisoning* by nitrate of silver (lunar caustic) is rare; in the majority of cases it is caused by the breaking off and swallowing of pieces of the caustic during cauterization of the throat; very rare are cases of poisoning caused by the ingestion of solutions of nitrate of silver taken with suicidal intent or accidentally. The fatal dose is not fixed. Nearly one ounce in solution has been taken without fatal result, and doses of nearly fifteen grains daily were formerly given therapeutically. The symptoms are those of corrosive gastritis, with occasionally cerebral disturbances. In one case (that of a child), death occurred at the end of nine hours.

Post-mortem appearances.—Inflammation in the upper part of the alimentary canal, extending downwards to the jejunum, the affected parts being blackened.

2. *Chronic poisoning.*—This is observed only as the result of the medicinal use of nitrate of silver, usually from its internal administration, but also from long-continued application of it to the throat as an escharotic, some of the fluid being swallowed. In the first case well-defined symptoms are not produced until its

use has been continued for months, and from two and a half drachms to three ounces have been taken.

The first sign of chronic silver poisoning is the appearance of a bluish line upon the gums similar to that produced by lead. The most important symptom is the so-called argyria—that is, the discoloration of the skin and mucous membranes. The skin assumes a grayish-blue color of greater or less intensity, which color is, as a rule, deeper on the cheeks, and generally on those portions of the body exposed to the light. The color increases in intensity for some time after the discontinuance of the remedy.

In addition to this peculiar color, symptoms of chronic gastro-intestinal catarrh and, in some cases, albuminuria have been observed as results of chronic silver-poisoning.

The discoloration is very permanent, and may last for years without change.

Post-mortem examination shows that the discoloration is not limited to the skin and superficial mucous membranes, but may extend to the liver, spleen, kidneys, intestinal mucous membrane, etc. Microscopic examination shows a deposit, probably of metallic silver, in the form of very fine granules, in the most superficial layers of the corium, in the sweat-glands, in the smooth muscular fibre, and in the capillaries of the skin. In the internal organs the deposit is chiefly in the walls of the smaller arteries, to a less extent in those of the veins, sometimes in the capillaries, the Malpighian corpuscles of the kidneys, etc. An abundant deposit of silver is also found in the interstitial tissue of the lymph-glands (mesenteric). The epithelium of the skin, as well as that of the internal organs, remains free to a marked extent.

Theoretical and Experimental Considerations.

According to Lieberkuehn, the nitrate of silver forms, when added to a solution of albumen, an albuminate of silver which contains 6.5 per cent. of silver. It is assumed by some that the silver is absorbed as such. There is no doubt that the albuminate of silver acts as a poison when it is injected or when it is

taken internally, but the manner in which it acts is not yet fully established. On the other hand, Riemer shows that by far the largest part (as much as nineteen-twentieths) of the nitrate of silver introduced into the stomach, as when taken medicinally, does not act as such, but is reduced in the stomach into an insoluble form, probably to metallic silver. R. considers, therefore, that in argyria the question is chiefly concerning the deposition of the silver granules already existing in the intestine. In opposition to this it should be observed that the distribution of the silver granules in that case is not similar to that of other pigments introduced into the body. At all events, we cannot, as was formerly done, refer the discoloration of the skin entirely to the reduction of the silver under the influence of light, although this was, perhaps, in some cases, noticeable, on account of the deeper color in those parts of the skin which were exposed to the light. Silver has been detected chemically in the organs in such cases of argyria. Silver is eliminated with the urine in cases where it has been administered for a long time, and even for some time after its administration has ceased.

Treatment.

In acute poisoning the white of eggs and milk should be given. Common salt is an antidote. It should be remembered that, when solid pieces of the poison have been swallowed, an attempt should be made to dissolve them.

Nothing is known concerning the treatment of argyria.

CHAPTER V.

MERCURIAL POISONING.

Overbeck, Mercur u. Syphilis. Berlin, 1861.—*Kussmaul*, Untersuchungen über den constitutionellen Mercurialismus. Würzburg, 1861.—*Baerensprung*, Annalen der Charité, VII. 1856.—*Voit*, Physiologisch-chemische Untersuchungen. Augsburg, 1857.—*Waller*, Prager Vierteljahrschrift. 1859 und 1860.—*Lorinser*,

Wiener medicinische Wochenschrift. 1859 u. 1860.—*Oettinger*, Ibid. 1859.—*v. Boeck*, Zeitschrift für Biologie. 1869.—*Saikowski*, Virchow's Archiv. 37.—*v. Oettingen*, De Calomelanos, etc. Dorpat. Dissert. 1848.

In cases of poisoning mercury cannot be detected in the organic fluids and tissues by the ordinary reactions, until after the destruction of the organic matter by hydrochloric acid and potassium chlorate; in performing this operation too high a temperature must be avoided, since all of the compounds of mercury are very volatile;—this process should be conducted over a water-bath at a moderate temperature. For the same reason the organic matter cannot be destroyed by incineration.

From the fluid thus obtained the mercury can be isolated by the methods used in inorganic analysis. The use of electrolysis is very highly recommended by Overbeck and others: the passage of a galvanic current (2–10 Bunsen or Grove cells) through a solution containing only one part of mercury in 40,000, gives a very plain coating of mercury upon a small gold plate attached to the negative electrode. Schneider was able to detect in this way one-sixth of a grain of corrosive sublimate dissolved in 500,000 times its weight of water. A piece of copper foil in the place of the gold foil gives a little less delicate results. In either case the nature of the deposit upon the metal should be tested by sublimation. For this purpose it should be introduced into a glass tube closed at one end. Upon the application of heat the deposit disappears from the metal, and is condensed upon the cool part of the tube in the form of a metallic mirror. This operation should be performed immediately after the deposit has been obtained by electrolysis, since otherwise the mercury might volatilize spontaneously. Mayençon and Bergeret have recently recommended for the detection of mercury a very simple electrolysis; moreover, they do not previously destroy the organic matter. So far as we know, their methods have not been confirmed by other investigators.

Stannous chloride precipitates the mercury, which always exists in the fluids resulting from the decomposition of the organic matter as corrosive sublimate, in the form of calomel, and, if an excess of the reagent has been added, in the form of metal-

lic mercury ; by means of this reagent mercury may be detected in solutions containing only one part in 40,000.

The poisonous action of mercury and its compounds is manifested in very different ways ; and this difference is not well defined by distinguishing between an acute and chronic form.

1. *The Corrosive Action of Mercurial Preparations upon the Intestinal Tract.*

Corrosive sublimate is almost the only preparation of mercury which is the cause of dangerous corrosion, and this may be taken as the type of the other mercurial compounds which have a similar action. It is rarely used with criminal intent, more frequently with suicidal, and very rarely is it the cause of cases of accidental poisoning. Excepting this compound, mercuric nitrate is the most frequent source of accidental poisoning. In its action it scarcely differs from corrosive sublimate. Corrosive sublimate is soluble in water, alcohol, and ether. It produces a precipitate in solutions of albumen even when very dilute. This precipitate appears to be a mercuric albuminate (see below under "Theoretical Considerations"). The powerful corrosive action of the sublimate seems to depend upon this property of uniting chemically with albumen.

The smallest fatal dose of corrosive sublimate is given as a little less than three grains for a child, and also for an adult. On the other hand, it is said that sometimes, and especially after its habitual use, as, for example, in the sublimate eaters of the East, enormous doses can be taken without injury ; in the same way it is said that an opium-eater, in addition to his usual quantity of opium, has taken daily two scruples of sublimate. The ingestion of corrosive sublimate in the same way as that of opium appears to be quite common, and its action to be similar to that of opium, only more exciting.

Clinical History.

On taking corrosive sublimate, its peculiar sharp and metallic taste will usually be noticed ; it produces powerful corrosion of

the mucous membrane of the mouth, œsophagus, stomach, and intestines, and leads rapidly to gastro-enteritis of the severest form.

Pain is felt in the mouth, throat, œsophagus, and stomach, and there is violent vomiting and diarrhœa characterized by numerous discharges which are attended with painful tenesmus. These are more frequently bloody than in arsenic-poisoning. In addition there is suppression of urine, often complete anuria, so that in two and even more days not a drop of urine will be passed—in arsenic-poisoning this rarely happens to the same extent; there is also the greatest prostration, and all of the symptoms of collapse, etc. In many cases the corrosive action of the poison affects the larynx, producing hoarseness and dyspnœa.

The *progress* of the case is usually very rapid. In one case (Taylor) death took place in half an hour; more frequently it occurs in from two to twelve hours, but in most cases after twenty-four hours. Rarely life is prolonged for ten or twelve days. In those cases in which the patient lives more than twenty-four hours, salivation frequently occurs, but this may be entirely wanting.

A favorable termination can scarcely be hoped for in the severer cases, where treatment is not resorted to immediately; in this respect, of course, in addition to the size of the dose, the condition of the stomach, whether full or empty, is an important feature.

The *post-mortem appearances* are those of corrosive gastro-enteritis; the mucous membrane of the mouth, throat, and œsophagus is inflamed, wrinkled, and covered with a white coat. The mucous membrane of the stomach is in some places, especially near the pylorus, converted into dark, very tough eschars. In some cases ulceration takes place; after separation of the eschars there may be perforation. Here and there particles of the substance used may be found adhering closely to the mucous membrane. In the small intestines the appearances are usually normal, but in the large intestine, on the contrary, severe inflammation, even to ulceration and hemorrhage, has frequently been noticed. This last appearance is to be looked upon as the begin-

ning of the general action of the mercury. In acute mercurial poisoning, mercury can usually be detected in the organs, but cases are known where death did not take place until the fourth day or later, in which not even a trace of mercury could be found in the organs, stomach, or contents of the intestines.

Treatment.—Freshly precipitated hydrated ferrous sulphide (Bouchardat and others), prepared by adding alkaline sulphides to a solution of ferrous sulphate, is the only substance which is universally acknowledged as a positive antidote, but it can rarely be obtained quickly enough. When vomiting has not taken place immediately, it should be produced by mechanical irritation, subcutaneous injection of apomorphia, etc.; the corrosive action of the sublimate should be counteracted by giving large quantities of milk, etc. It must not be forgotten that the compound of the mercury with the albumen thus formed (see above) is soluble, and must be removed.

The use of the stomach-pump has been pretty generally, but probably erroneously, condemned, for fear of possible perforation on account of the great corrosion of the œsophagus and stomach.

2. *Mercurial Poisoning by Absorption of the Poison into the Circulation.—Constitutional Mercurial Poisoning.*

With the exception of cinnabar (simple sulphide of mercury), which acts only in the form of vapor, all of the preparations of mercury, when taken into the system, have a poisonous action. The only doubt about this is in regard to metallic mercury.[1] The experiments of Overbeck, however, seem to have settled this question. These were made with mercurial ointment. According to these investigations and those of others, there is no doubt that, when energetically rubbed into the skin, the finest particles of mercury penetrate into the subcutaneous cellular tissue, and thence into the circulation in large amount; yet the action of this ointment has been ascribed to the fatty mercurous salts which it always contains. This may, doubtless,

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[1] See *Hermann*, Experimentelle Toxicologie.

explain a part of the action of old ointment (which contains a large amount of mercurous salts), but Overbeck found too slight a difference in the action of such old ointment and that freshly prepared from chemically pure metallic mercury, to be able to disregard entirely the action of the absorbed metal. The fact that metallic mercury can be taken into the stomach in large amounts, from three to nine ounces and more, without giving rise to poisoning, shows only that the metal is harmless in those cases in which a small surface is exposed to the oxidizing action of the system.

The ways in which mercury may get into the body are very various. First in importance are its therapeutic uses. Mercurial ointment is a form much used at the present time; also the subcutaneous injection of corrosive sublimate solutions, and the internal administration of calomel, less frequently of corrosive sublimate (Dzondi), play an important part. Many other mercurial preparations are still used internally by older physicians, such as mercurous iodide (hydrargyri iodidum viride, U. S., Br.), and much more rarely mercuric iodide (hydrargyri iodidum rubrum, U. S., Br.). In England metallic mercury is much used internally in the form of blue-pills. Externally many different preparations are used, according as they are more or less irritant, in the form of plasters, and corrosive sublimate solutions are frequently added to baths and poultices. Inunctions of cinnabar are rarely used at the present time. All of these methods may give rise to the most severe mercurial poisoning if employed energetically enough; even applications to the undenuded skin may have this effect, which is produced much more readily if the application is made to an ulcerated surface.

In the use of mercury in the arts, in addition to the dust which contains particles of mercury or a mercurial compound, we must consider the vapor of mercury as of the most importance, especially when the work is performed at a high temperature, but also even at a very low temperature. Those who are, by virtue of their work, most endangered are workers in quicksilver mines and smelting works, manufacturers of mirrors, gilders, manufacturers of thermometers, percussion-caps, etc.; in a less

degree hatters, bronzers, and furriers. Some time ago much excitement was created by the accidents which happened to sailors upon certain vessels in which during the voyage jars, containing metallic mercury, became leaky; the mercury, which was spilled in the hold of the vessel, gave rise to the most severe symptoms of poisoning. Those cases are similar in which, in working with mercury, the metal accidentally falls to the floor and gets into the cracks. Cases of mercurial poisoning, as a result of this apparently, are not rare. In the same way persons have been poisoned from living in rooms in which mercury was spilled many years before; also persons who live in the neighborhood of rooms thus infected. It does not appear that the public is at all endangered by the illegal use of mercurial compounds for adulterating articles of food, or in the manufacture of articles for general use.

The action of mercurial compounds, especially the therapeutic action, varies very much in intensity and in kind; this variation depending largely upon the conditions—on the one side of the preparation and on the other of the organism—affecting its absorption. The more easily soluble compounds, besides being more irritant, are also more readily absorbed; but those which are soluble with the greatest difficulty, like metallic mercury, can also be absorbed, and are by no means absolutely inert as regards the irritant action. With reference to this subject the investigations begun by Buchheim (Oettingen), and continued by Voit and Overbeck, are especially important.

All mercurial salts, even metallic mercury itself, are, as already mentioned, when in a state of sufficiently minute subdivision, converted more or less readily by contact with the alkaline chlorides, especially when albuminous compounds are also present, into corrosive sublimate, which is easily soluble and is a powerful escharotic. This change is apparently hastened by the presence of free hydrochloric acid. As the general action of the insoluble preparations of mercury depends entirely upon this change, so also do many of the local effects; as, for example, the irritating and purgative action of calomel is solely dependent upon this conversion into corrosive sublimate; in this way very unusual effects of calomel become intelligible. Thus we have

reports of cases in which most violent and fatal mercurial stomatitis has been produced by very small doses of calomel; as, for example, very severe stomatitis, lasting for weeks, with necrosis of the jaw, was produced in a boy eight years of age, after taking once a day for three days a dose of three-fifths of a grain of calomel; in another case a boy fourteen years old (?) died from mercurial poisoning (necrosis of the lower jaw) produced by one dose of five and a half grains of calomel. Many cases are reported in which fatal stomatitis has been caused by from six to fifteen grains of calomel taken during twenty-four hours, or in a single dose. The same is true of metallic mercury. Fatal cases have been reported in England caused by taking, for example, in the course of a week, about fifteen grains of mercury with chalk, or the same amount of blue-pill, which contains at the most only a few grains of mercury. We must assume that in these cases the change of the calomel or the metallic mercury into corrosive sublimate, which usually takes place only to a slight extent, is very much greater, perhaps owing to the presence of an unusually large amount of free hydrochloric acid, etc. It cannot be denied, however, that in addition to the above-mentioned points in reference to the poisonous action of mercury and its preparations, different individuals show a very varying susceptibility to them. The fact that, of the workmen exposed to the fumes of mercury, some remain entirely free from any injurious effects, bears testimony to this. Furthermore, it can be easily shown that mercurial ointment, applied to the skin of many persons, even in very small amount and superficially, as for the destruction of crab-lice, always produces very severe symptoms. An instructive case is reported by Alfinger (Kussmaul) of a girl who was affected with mercurial stomatitis caused by simply rooming with her sister, who was employed in manufacturing mirrors, and who remained entirely unaffected herself. To explain the above-mentioned cases of poisoning by small doses of calomel, etc., individual predisposition must be taken into account in addition to the other points mentioned. It has been repeatedly stated that young people are more apt to be affected than older ones.

Usually the symptoms of poisoning by mercury come on while the individual is still exposed to its action, but it some-

times happens that they are entirely absent during this period and do not appear until after removal from its influence. Several cases are reported in which the symptoms which first appeared in the disease were repeated later, and also returned again after the lapse of years without any re-exposure of the individual to the action of the poison. This has been the case with salivation after one attack of mercurial stomatitis, caused either by the use of mercury in the arts or by its therapeutic administration, and is especially true of mercurial palsy. In one case of Kussmaul's there appeared, after handling mercury (making mirrors) for nine months, severe palsy, which, although the patient was removed from the influence of the mercury, constantly recurred with varying intensity during a period of twenty-five years.

Clinical History.

Formerly, and even at the present time, the severest diseases, especially ulcerative diseases of the skin and affections of the bones, have been ascribed to mercurial poisoning. We do not in recent times see affections of the bone occurring as symptoms of the action of mercury, and their existence in former times has never been fully demonstrated. Also special mercurial skin diseases, severe ones at least, have not been recorded since Alley's extended reports. The reports and descriptions of the so-called hydrargyria rest in the main, doubtless, upon mistakes and erroneous diagnoses.

Eczema is, however, frequently observed after mercurial poisoning, but apparently as the result chiefly of the local irritant action of the preparation used upon the skin, or occasionally as the result of copious perspiration, uncleanliness, etc.; but this, and still less the abscesses which sometimes follow the subcutaneous injection of corrosive sublimate, cannot be regarded as symptoms of mercurial poisoning. It should not and cannot be denied that formerly these, as well as all other possible consequences of mercurial poisoning, were observed; yet in those cases the condition was not one of simple poisoning, but, in consequence of the rashly excessive mercurial treatment, symptoms of poisoning were produced, and, at the same time, the system

was reduced to the greatest degree, partly by this treatment, and partly by attacks and influences entirely independent of the mercury. The symptoms which were observed in such individuals, cachectic and usually syphilitic to begin with, could not truly be unequivocal.

In the consideration of ordinary constitutional mercurialism we will except entirely those rare cases, in which very acute poisoning is caused by a single application of corrosive sublimate to the skin or to an ulcerated surface. Thus, in the cases of two men, fatal poisoning followed the application of an ointment (one ounce of corrosive sublimate in six ounces of lard) for the itch, and the same number of fatal cases resulted from the application of an ointment consisting of two drachms of corrosive sublimate in an ounce of fat for disease of the scalp. There was, it is true, in these cases a general and not a local action of the poison, for they ran exactly the same course as a case of acute poisoning from the internal ingestion of corrosive sublimate—that is, with the most violent acute gastro-enteritis and death in a few days; the post-mortem appearances also were exactly the same as in acute sublimate poisoning.

If we leave out of account the doubtful results of mercurial poisoning and these forms allied to acute sublimate poisoning, then poisoning by mercury assumes the following simple form:

Of the greatest importance is the influence of the metal upon nutrition; this is rarely wanting when the action of the mercury is severe. Where small quantities of mercury are absorbed during a long period, as in cases where the daily handling of mercury, in one's occupation, leads to poisoning, this action of the mercury shows itself usually by a simple anæmia; this appears more rapidly when relatively large amounts are absorbed in a shorter time, as in the so-called mercury cures. In these cases also we have a simple anæmia characterized by a pale color of the skin and mucous membranes, lassitude and malaise combined occasionally, as is frequently the case in anæmia, with so called rheumatoid pains. In other cases this comes on with a more or less intense fever, which is, however, rarely of much consequence. Besides the symptoms due to this, there are usually observable signs of a chronic gastric catarrh and of a genuine enteritis:

diarrhœa, often accompanied by very violent colicky pains, tenesmus, and evacuation of slimy and even bloody discharges.

This enteritis is caused as well by the external application of mercury in the form of gray ointment (Brandes) as by the internal ingestion of mercurial compounds. When the general action develops more rapidly, salivation has usually been observed before the appearance of the above symptoms; this is a sign of the specific mercurial affection, stomatitis. This is, however, in an especially high degree, dependent upon whether the proper precautions have been taken to prevent its appearance or not. In cases where this has been done, salivation frequently fails to appear, even when the other symptoms of poisoning are present. Otherwise, or sometimes in spite of all precautions, salivation is sometimes the first symptom of poisoning. It begins almost without exception with an abundant flow of saliva, fetor of the breath, and simultaneous swelling of the gums, upon which, when the affection is severe, there appears a croupous membrane; this is at first lightly attached, but later it adheres more closely and an ulceration of the gum develops beneath it; this can also occur without previous exudation. These changes take place first in those spots where particles of food or the secretions collect and remain, as in the folds of the membrane, at the edge of the teeth, especially when carious or unclean, and in the fold between the gum and cheek. The ulcerations may, when long neglected, or in especially unfavorable cases (more easily in children and after or simultaneously with a severe acute febrile disease), increase in extent and lead to extensive destruction of tissue, even to necrosis of the jaw.

In such cases the disturbance of nutrition may reach to any extent, and a high fever, accompanied with general collapse, may develop, as well as brain symptoms and conditions of a scorbutic nature with tendency to hemorrhages, etc.; in these cases it cannot be determined exactly how far the symptoms are dependent upon the direct action of the mercury.

It is very rare that the above disturbances of nutrition reach to such a dangerous extent in acute mercurial poisoning without the addition of severe stomatitis.

Very different is that form of mercurial poisoning which

comes on very gradually, as in workers in mercury mines, mirror and thermometer manufacturers, etc. In these cases the same symptoms usually develop, only more slowly, but unfortunately there are present as signs of mercurial poisoning, often for years, a more or less severe gastric and intestinal catarrh, a gradually increasing anæmia, a moderate increase of the salivary secretion, a peculiar tendency to stomatitis, and the so-called mercurial erethism.

The general character of this last symptom is very peculiar. Essentially the condition is characterized by great mental excitability of the patient to external impressions. Every unexpected or perplexing event excites him in the highest degree. The visit and conversation of the physician put him into a state of complete bewilderment, even to syncope; the adult patient grows pale, and stammers in answering the simplest questions. To perform his allotted task requires the greatest effort, or is even impossible if he sees or thinks that he is being watched. There is also great solicitude and a feeling of anxiety without any reason for it. There is sleeplessness, or sleep which is restless, frequently broken, and disturbed by frightful dreams, headache, and palpitation. In the severer forms there are frequently hallucinations, usually of a frightful nature. When perplexed or excited, traces of tremor are often perceptible in a slight twitching of the muscles of the face at the corners of the mouth.

Such a condition of slight intensity may last for years or tens of years, and may then be characterized as an habitual mercurialism.

Usually after this condition has lasted for weeks, or sometimes for years, mercurial tremor comes on.

This is very different, especially in its intensity, from the similar conditions which one sees in chronic poisoning by lead and other metals; when severe, it resembles almost exactly paralysis agitans. It begins in the upper extremities, tongue, and muscles of the face, and extends to the lower extremities. It comes on as a slight quivering, perceptible especially on speaking, and increases gradually in violence until complete convulsive twitchings are produced. These convulsions, although existing in all parts of the body, differ from the so-called general convulsions

by appearing in the single limbs independently. They render locomotion impossible.

During sleep the trembling ceases completely; any attempt to move increases it or brings it on; excitement of any kind, especially mental emotion, also strengthens it. In the severe grades of tremor, paralysis of the affected limbs always occurs. This is always more severe in the lower extremities; it reaches a high degree first in the later stages. Paralysis without tremor scarcely ever occurs; but cases have been repeatedly observed in which, after long duration of the tremor, paralysis occupies the prominent position, the trembling being diminished.

In one case, six weeks before death, there was observed entire cessation of the tremor and the simultaneous appearance of complete paralysis of both legs and the right arm; the paralysis of the arm became better. Kussmaul describes a case in which, after severe mercurial tremor and clonic spasms, permanent paralysis of the right arm developed itself.

Anæsthesia has not been observed as a result of the action of mercury; but, on the contrary, pain, in part purely neuralgic, of the most varying kinds is a frequent consequence of the poisoning: very violent, even insupportable headache, partly in connection with the stomatitis; toothache, and maxillary neuralgia; dragging and tearing pains in all of the limbs without any visible evidence of inflammatory lesion. There is a feeling of oppression in the chest, increasing even to attacks of asthma, without any disease of the thoracic organs being demonstrable.

Much stress has always been laid on the mental anomalies in mercurialism, but the cases which have been cited are of very doubtful value, syphilis and other conditions of the greatest importance in the causation of mental diseases playing their part. Yet what has been mentioned above of mercurial erethism shows satisfactorily the peculiar action of the metal upon the mental condition. The mental disease, however, hardly equals the description there given; at all events, peculiar and well-defined conditions of mental alienation develop themselves very rarely, but tolerably severe mental weakness, with diminution of memory, etc., is not very infrequent.

The same is true with regard to the existence of apoplexy and

mercurial epilepsy. Authentic cases of the former appear to be unknown, and cases of true epilepsy have not been established with certainty, although cases of syncope with an aura (epileptoid syncope) have been observed.

Overbeck is of the opinion that it must remain undecided whether these conditions are directly caused by the mercury, or whether it be not the cachexia developing more and more under the influence of the poison that should be considered as their cause.

All of these conditions, and also the severe symptoms of mercury-poisoning in general, are, if not of too long duration, capable of improvement; yet they may become permanent at any stage; thus the simple, often very severe trembling, due to the action of mercurial poisoning, is most frequently seen remaining through life.

In the later stages of the disease it frequently advances in spite of all treatment and of total removal from the influence of the poison, and death takes place with increasing cachexia or supervening phthisis.

It frequently recurs in the less advanced cases.

Of the complications which occur in persons suffering from mercurial poisoning, and which stand in distant relation to it, must be mentioned first of all pulmonary phthisis, which, according to Kussmaul's reports, exists very frequently, and causes by far the greatest number of deaths in constitutional chronic mercurialism. Pregnant women are said to miscarry very easily, and children frequently become feeble, scrofulous, or rachitic, or are born otherwise diseased. The existence of salivation or of the tremor in new-born or very young infants, when the mothers were severely affected with mercurial poisoning, is of interest. So far as known, however, the direct influence of the mercury upon the child cannot be excluded in a single case, since the mothers were in all cases, owing to the nature of their occupation, exposed to what is termed "professional" poisoning, and it is probable that they carried the metal in their clothing or otherwise, from the shops to their own or their children's room.

In those who are severely affected, dropsy may develop itself

and prove fatal; nephritis appears to cause this very rarely, although temporary albuminuria is not rare in severe chronic constitutional mercurialism.

Theoretical and Experimental Considerations.

The constitutional action of all of the preparations of mercury, with the exception perhaps of mercuric nitrate, presupposes their change into corrosive sublimate. That this is the case with metallic mercury and the iodides, as well as with calomel, has been, in spite of many contradictions even at the present time, proved by Voit's experiments, which were based upon the older work of Mialhé. This change takes place, even at the temperature of the body, under the influence of the common salt and the albuminous compounds. Whether these act as carriers of ozone, as Voit thinks, must remain unsettled. Corrosive sublimate forms with the albuminous substances a mercuric albuminate, which is insoluble in water, but soluble in an excess of albumen; in this compound the mercury is probably contained in the form of mercuric oxide. The mercuric albuminate absorbed into the body appears to be distributed through all of the organs, and can frequently, if not always, be detected in them in constitutional mercurialism. No quantitative estimations of the mercury in the organs have been reported. Mercury has certainly been found in the liver, when the person had not been exposed to its action for a year. It has been proved by the reports of good observers, that mercury exists relatively very often in the bones in accumulations readily discernible by the naked eye even many years after mercurial treatment. The metal has also been occasionally found in biliary calculi, as I can certify from my own observation. It must not be considered, however, from the finding of metallic mercury in the bones, that the mercuric albuminate taken into the body has been decomposed by reduction of the mercuric oxide and the deposition of the metal, since it is not proved that this condition exists, except when the metal itself has been applied (inunction), and it may very well be a simple accumulation of the mercury which has been absorbed as such, and not converted into the albuminate. Yet it is certain

that the mercuric albuminate in the body is again decomposed, this is shown by the fact that the mercury is sometimes eliminated in urine which does not contain albumen. Frequently, however, we find the urine albuminous when it contains mercury Besides with the urine, mercury is eliminated with the saliva, bile, fæces, and perhaps the sweat. Bergeron and Lemaitre observed an elimination of mercury with the sweat after giving mercuric iodide. Voit asserts that he has observed in the case of a thermometer-maker, who was suffering from severe mercurial cachexia, that articles of silver were amalgamated by being in contact with his hands; Kussmaul, on the contrary, could detect no mercury in considerable quantities of the sweat of a mirror manufacturer similarly affected. This elimination of the metal in the form of the finest globules has been observed in the urine, fæces, and bile, after inunction. The elimination may, as is probable in the case of the urine, be intermittent, and be going on years after the absorption. In other cases, no mercury was found in the organs several weeks, or even only one week, after taking a moderate amount; it is possible, therefore, that the elimination was already completed at the expiration of that time.

Little has been determined theoretically or experimentally concerning the influence which mercurial poisoning exerts upon the metamorphosis of tissue in the organism. The investigations of Boeck seem to show that mercury neither increases nor diminishes tissue-metamorphosis in general, but, according to Saikowski, who experimented with animals (rabbits and dogs), corrosive sublimate causes an increased secretion and a saccharine condition of the urine of long duration. To mercury, and especially to calomel, has been ascribed the power of increasing the biliary secretion, but this result has not been noticed by most observers experimenting upon dogs with biliary fistulæ. Little is known concerning the cause of the single symptoms of mercurial poisoning. That the stomatitis is the direct result of the inflammation of the mucous membrane by the mercury contained in the saliva is not established, since careful investigators of many cases of mercurial salivation deny that mercury is generally present in the saliva. But the gastric and intestinal catarrh may be the

result of the irritation produced by the mercury eliminated into the contents of the intestine, and here, perhaps, changed partly into corrosive sublimate; at all events, the reports of many authors agree in this, that the elimination of mercury in the fæces is abundant and constant. It is not yet determined whether all of the mercury eliminated with the fæces (leaving out of account, of course, that which is taken by the mouth) comes from the bile or not. Nothing is known of those circumstances which cause the mercurial tremor, etc. In all probability it is due to an affection of the central nervous system, but the nature of this disease produced by the influence of the metal is thus far entirely unknown, and it is not proved that this specific result of the poison is due to the direct action of the mercury upon those portions of the brain whose functions are disturbed by it. It must not be forgotten that the presence of the poison in the diseased organ has by no means been detected in all cases of mercurial tremor, etc.

Concerning those diseases which stand in remote relation to mercury-poisoning, such as phthisis pulmonum, which is especially frequent in mirror manufacturers, there is no positive proof that they are the result of a specific mercurial action. The great activity of workers in mercury, with all of the dangerous influences which are associated with such activity, and also the anæmia and cachexia caused by the mercury, are the cause, and not the metal itself. This consideration should have an influence in deciding as to the advisability of employing mercurial treatment in many cases.

Treatment of Mercurial Poisoning.

The prophylactic treatment, of course, varies to an important extent, according to the form in which the poison comes in contact with the body. This is not the place to enumerate the means which must be used to prevent the appearance of dangerous symptoms in the energetic employment of mercurial treatment. To prevent professional mercurial poisoning all of those precautions should be taken which are generally employed in workshops where dangerous substances, and especially those giving

rise to dangerous fumes and dust, are used. First of all we should insist upon the most complete ventilation of the work-rooms possible, prohibition from taking food in the shop, cleanliness, such as washing the hands and changing the clothing on leaving work, etc., etc. In certain cases it is easy to form an opinion as to whether the conditions of sufficient ventilation are fulfilled, or whether there is danger from the diffusion of mercurial vapor or dust on account of defective ventilation in the work- or dwelling-rooms; living flowers serve as the most delicate reagent for detecting such dangerous impurities in the atmosphere; they die very quickly in an atmosphere containing mercury. A gold leaf becomes quickly amalgamated in such an atmosphere, and a stick of wood painted with flowers of sulphur becomes brown on the surface, owing to the formation of sulphide of mercury.

If not successful in keeping the atmosphere free from mercury, we would recommend as an experiment the free use of flowers of sulphur in some form, such as strewing it upon the floor, painting the walls with it, or as a sulphur respirator—that is, linen cloths, the meshes of which are filled with sulphur. It appears certain that the action of mercurial vapor upon plants at least is neutralized by saturating the atmosphere with sulphur, on account of the formation of the sulphide of mercury.

Recently it has been recommended to saturate the air of the affected rooms with ammonia vapor by sprinkling the floor with a strong ammonic hydrate solution after working hours. Experience is said to have found this procedure successful, although chemically it is not yet understood.

When the system is being subjected to the action of mercury, good food, and at the same time the use of warm baths, appear to be the best means of preventing the symptoms of poisoning. The importance of good food is equally great for both forms of poisoning—that caused by the therapeutic and that by the professional use of mercury. The general opinion of those who work with mercury in mirror manufactories appears to be, according to Kussmaul, that loss of appetite, and consequently diminished nutrition, favors very much the appearance of the severer symptoms, and, so far as therapeutic poisoning is con-

cerned, the most careful physicians consider loss of appetite in their patients to be the most positive contraindication against the energetic continuance of mercurial treatment.

The same means are also of service when the symptoms of poisoning have already appeared. Since the elimination of the poison by the skin is generally established, the cause of the favorable action of warm baths is explained by the increase of the secretion of the perspiration.

As a further means of hastening the elimination of mercury, the use of potassium iodide in large doses for a long time has been recommended as the result of very satisfactory experiments. These experiments, to be sure, are not entirely conclusive; yet it must be acknowledged that the numerous and closely agreeing investigations upon the elimination of mercury in general, or its increase in the urine in cases of mercurial poisoning, after the administration of potassium iodide, render the employment of this drug advisable.

For the treatment of the stomatitis the best means known is the most scrupulous cleanliness of the mouth.

Electricity has for many years been recommended in the treatment of the mercurial tremor.

CHAPTER VI.

ANTIMONY-POISONING.

Ackermann, Virchow's Archiv. Bd. 35.—*Nobiling*, Zeitschrift f. Biologie. Bd. IV.—*Saikowski*, Virchow's Archiv. Bd. 34.—*Buchheim* und *Eisenmenger*, Eckhard's Beiträge. Bd. V.—*Kleimann* und *Simonowitsch*, Archiv für Physiologie. Bd. V.

In order to detect antimony in the organs and fluids the organic matter must first be destroyed, preferably by hydrochloric acid and potassic chlorate.

Of the compounds of antimony almost the only one to be considered in toxicology is the familiar double tartrate of antimony and potassium, the so-called tartar emetic; in addition, however, a few cases are known of poisoning caused by the terchloride and the pentasulphide of antimony ("golden sulphide"). Cases

of poisoning by working with and using metallic antimony are said by van Hasselt to be frequent; yet in those cases where arsenic and other poisons are almost always present at the same time, it is very difficult to determine the part played by the antimony.

The majority of the cases of poisoning by tartar emetic are caused by its medicinal use, but more frequently by the use of patent medicines which contain tartar emetic in large amounts. There are also occasionally cases of accidental poisoning by tartar emetic. On the whole, it is rarely used for criminal or suicidal purposes.

From nine to fifteen grains is regarded as a fatal, or at least highly dangerous, dose for a healthy adult; van Hasselt gives as the fatal dose from two scruples to one drachm. Much larger doses, however, have been endured, and much smaller doses have been seen to produce very dangerous symptoms, as one-sixteenth and one-twenty-fourth of a grain (Taylor). In children, and in old or enfeebled persons, tartar emetic appears to act as an especially dangerous poison; death has resulted in children from taking about three-quarters of a grain, and in adults, under favorable circumstances, from taking a little less than two grains.

On the contrary, it has been taught for a long time and by the most eminent authorities, who, like Laennec, recommend the use of tartar emetic in acute inflammatory diseases, especially in pneumonia, that the system under such conditions "tolerates" the drug in otherwise incredibly large doses. As little as such a "tolerance" seems *a priori* credible, just so little has it been proved by sufficient experiment. The fact is, however, that not rarely enormous doses, an ounce and more, have been taken without fatal result; a fact which is not so difficult to understand, since the rapid production of vomiting and purging expels the largest part of the poison.

Little is known with certainty concerning the existence of a chronic form of tartar emetic poisoning, unless we consider as chronic poisoning the more or less severe gastro-intestinal catarrh produced by repeated attempts at poisoning the same person by large doses, or the occasional continued use of the drug in small doses. The experiments of Mayerhofer and Nobi-

ling upon themselves teach us that such is the result of the long-continued use of small, so-called nauseating, doses; other than this these chronic forms of poisoning show little that is important.

Clinical History of Acute Poisoning by Tartar Emetic

The symptoms are those of the most severe gastro-enteritis. From a few minutes to one-half an hour or an hour after the poisoning severe pain is felt in the mouth, throat, and along the œsophagus to the stomach, and there is violent vomiting, and a little later purging. In all cases in which the action of tartar emetic is powerful, and consequently in cases of poisoning, collapse soon appears, forming a prominent feature, and increasing to the greatest extent. In many cases it appears when the symptoms of gastro-enteritis are wanting or only slightly marked (such as vomiting once or only a few times), and where diarrhœa is absent.

Thus the case may resemble one of arsenic-poisoning, but in its farther progress it differs from the latter very materially. In fatal cases the deceptive remissions frequently seen in arsenic-poisoning are wanting, and recovery from tartar emetic poisoning is not rare, even when there is the greatest collapse with pulselessness, coldness of the extremities, etc. Convulsions are seen before death in fatal cases, and also occasionally in cases ending in recovery. One case, reported by Taylor (Mayer, Gleaves), is very peculiar; in this genuine tartar emetic pustules were said to have appeared in large numbers upon the skin on the third day after the poison was taken.

Death may take place within twenty-four hours, but usually it does not result until after the lapse of weeks.

It is not to be wondered at that severe chronic disturbances of the stomach are noticed as results of the poisoning.

The *post-mortem appearances* seem to be very different in different cases. The most important are those of gastritis, which are rarely wanting; in some cases this has reached the highest degree, and led to hemorrhagic exudation and infiltration upon and into the mucous membrane of the stomach, and even to

abundant hemorrhage into the intestinal canal. In several cases extension of the inflammation to the serous membrane has been reported. Slight ulceration of the mucous membrane has frequently been seen, and in some cases it has been found in the upper part of the small intestine.

The reports, as to the presence of antimony in the organs of individuals who have been poisoned, differ very much; it is certain that antimony appears quickly in the urine after the ingestion of small amounts of tartar emetic, and is eliminated with the urine in relatively large amounts. This elimination appears in some cases to be intermittent, as was mentioned above in the case of mercury. It frequently happens that none can be detected in the stomach even only a few hours after its ingestion, but at that time it always appears to be present in the liver, bile, and kidneys. It has also been detected in the milk (Lehwald); so that poisoning of infants (nurslings) may take place. It has been found in the liver of the fœtus when the mother had taken tartar emetic before delivery. It has also been found several times in the bones a long time (four months) after taking the poison. Of especial importance is the statement of Taylor, that he has found the antimony in the tissues in a form soluble simply in water.

Theoretical and Experimental Considerations.

Reference has already been made to the absorption and elimination of tartar emetic. It should be added that large amounts of antimony have been detected in the vomited matters after the injection of the drug under the skin or into the veins. Hermann relies upon this fact not to commit himself to the statement that the vomiting produced by tartar emetic is independent of the local action of the drug upon the mucous membrane of the alimentary canal. Magendie observed that retching was produced by injection of tartar emetic into the veins of dogs after extirpation of the stomach; the supposition remains possible, however, that the drug was eliminated by the mucous membrane of the intestine, and exerted its local action; and in favor of this supposition is the fact that as large doses are necessary to produce vomiting when injected into the veins as when taken into the

stomach. These facts are not without value also for the interpretation of precisely the same conditions in arsenic-poisoning.

It is not yet established whether all of the antimony eliminated into the intestine comes entirely from the bile or not. Whether and how far the collapse—the feeble action of the heart —which is a very prominent symptom, is caused by the gastro-enteritis, cannot be determined with certainty. There is no doubt that tartar emetic is a powerful cardiac poison; the cessation of the heart's action, which is observed in experiments, is at all events independent of the influence of the poison upon the central nervous system, since it takes place also after destruction of the medulla oblongata.

Concerning the relation of the different constituents of this compound to its action, it is only known that the paralysis of the heart is in no way to be ascribed, as Nobiling thought, to the potassium which it contains, since tartrate of sodium and antimony acts with almost equal power, and the tartrate of antimony alone has a similar, though somewhat weaker, action. Antimony, therefore, appears to be the principal active ingredient.

The action of tartar emetic upon the tissues is similar to that of arsenic; it produces violent inflammation when applied to the external skin as well as to the mucous membranes, but it is not a true corrosive, since it does not destroy the tissues by directly producing new chemical compounds, or by the extraction of water, or by simple solution.

Among other experimental facts, we must notice that Saikowski has observed, after poisoning with antimonic acid, and to a still more marked degree after poisoning with the terchloride of antimony, the same changes in the glandular organs and in the muscular tissue of the heart, as those which are seen after poisoning with phosphorus and arsenic. In many localities, it is said to be the custom to put gray antimony into the drinking-water of geese which are being fattened, in order to produce a very fat liver (Grohe and Mosler). A similar treatment of fowls is said to have been known centuries ago (Husemann).

Treatment.

As an antidote to tartar emetic drugs containing tannic acid should be given, preferably in the form of decoction ; decoction of cinchona is frequently administered. The inflammatory action of the poison should be counteracted by surrounding it with albumen, milk, etc.

In the more chronic form of poisoning, potassium iodide has been given, it having been assumed, from its analogy to poisoning by mercury and other metals, that this drug favors the elimination of the poison.

CHAPTER VII.

RARER FORMS OF POISONING BY THE HEAVY METALS—IRON, MANGANESE, CHROMIUM, TIN, BISMUTH, GOLD, THALLIUM, AND OTHERS.

Quincke, Archiv für Anatomie und Physiologie. 1868.—*Pokrowski*, Virchow's Archiv. 22.—*Paulet*, Archives génér. 1863. — *Linstow*, Vierteljahrschrift für gerichtliche Medicin. 1874.—*Mayençon* und *Bergeret*, Canstatt's Jahresbericht. 1873.—*Lebedeff*, Canstatt's Jahresbericht. 1869.—*Stefanowitsch*, Ibid.—*Marmé*, Göttinger Nachrichten. 1867.

a. Poisoning by Salts of Iron

is a very rare occurrence ; yet cases of criminal, suicidal, and accidental poisoning have occurred. The only preparations of iron which are poisonous are : ferrous sulphate, ferric chloride (in the form of the solution [and tincture]), and occasionally the tannate of iron in the form of ink.

There are not a sufficient number of facts to enable us to fix the fatal or dangerous dose. Ferric chloride and ferrous sulphate appear to act with about the same severity; in fatal cases they were taken in doses of more than an ounce; yet, according to Orfila's experiments upon dogs, much smaller doses would suffice.

We must, of course, separate the cases of true poisoning from those not rare cases, in which the medicinal use of some of the iron preparations has resulted in some disturbance of digestion, since otherwise we would be led to formulate a chronic form of iron-poisoning, and, in fact, these symptoms have occasionally been described as such.

As an altogether doubtful curiosity, we find reported a case of iron-poisoning from the external application of the preparation. This was the case of a boy who had worked with his hands in a solution of ferrous sulphate. After long-continued work of this kind, vomiting and purging came on as symptoms of the poisoning.

The *symptoms* of poisoning by the above iron preparations are a toxic gastritis of slight intensity; the matters vomited and, of course, the fæces are colored black, from the presence of the sulphide of iron.

The *post-mortem appearances* are not characteristic; the greenish-black discoloration of the mucous membrane mentioned in some cases seems to have no connection with the poisoning.

Theoretical and Experimental Considerations.

The inflammatory action of the above salts of iron depends mainly upon simple corrosion. The ferric salts, and especially the chloride, coagulate albumen, and the same is true of the ferrous salts also, but only because they are in part, in the body as well as in the air, quickly changed to ferric compounds.

The iron preparations are eliminated with the urine; they exist in this fluid partly in the form of ferric and partly in the form of ferrous salts, no matter whether the former or the latter were ingested. The statement of van Hasselt, that the elimination of iron, especially when it has been taken in small doses, does not begin for a long time, is very peculiar. Iron is said also to be eliminated with the milk.

Ferric salts injected into the blood act as an intense poison; ferrous salts also are quickly oxidized, and produce coagulation of the blood, and consequently death from embolism. If injected very slowly in small amounts, only minute coagula are produced;

these are taken up by the white blood-corpuscles, and distributed throughout all of the organs; if the organs are treated with sulphide of ammonium, a green color (macro- and microscopic) is produced, which permits the detection of the presence of these iron-containing cells.

Some of these salts of iron, such as the citrate, leave the organism in the urine unchanged. Pokrowsky found that the amount of urea in the urine of patients after taking iron was increased, and that there was a slight increase of the average temperature of the body. Unfortunately his experiments have not been repeated.

b. Poisoning by Preparations of Manganese

has practically no importance. The experiments of Laschkewitsch[1] show that they differ very much from the iron salts. According to him they are very poisonous, and cause death by paralysis of the heart.

c. Poisoning by Preparations of Chromium.

Of these only chromic acid and its salts, the neutral chromate and bichromate of potassium, and the chromate of lead (chrome yellow), need be considered in reference to poisoning.

Cases of acute poisoning by these preparations are chiefly accidental or suicidal, and are very rare; chronic chromium-poisoning has been noticed in workers who handle solutions of the chromates or chromic acid, or who are exposed to the action of the dust from these compounds; those who are exposed to the action of the dust suffer from ulceration of the hands, which heals with difficulty, or of the mucous membrane of the nose, or of the scrotum, and other places. The chromate of lead has given rise to two cases of fatal poisoning in children who ate confectionery colored with it.

The fatal dose of chromic acid and that of potassium bichromate appear to be the same, but that of the neutral potassium

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[1] Centralblatt für die medicinischen Wissenschaften. 1866. Vorläufige Mittheilung

chromate is larger, while that of the chromate of lead is very small. All of them produce death in doses of a few grains. The symptoms in the majority of cases are those of severe corrosive gastro-enteritis, which is evidently caused by the escharotic properties of the preparation. It is remarkable that in a number of the fatal cases the gastric and intestinal symptoms were almost completely wanting, and that the

Post-mortem appearances in some cases consisted only of unimportant changes in the gastro-intestinal mucous membrane; usually, however, ulceration or softening of the mucous membrane of the stomach was found. In some cases this change extended to the jejunum.

d. Poisoning by Compounds of Tin

is of the greatest rarity. Only two authentic cases are known.

Frequently, poisoning of a mild grade is said to be caused by eating acid or fatty articles of food which have been kept in tin or tinned vessels, owing to the solution of the metal; it is to be remembered, however, that tin is very frequently contaminated with lead, copper, and arsenic, or that alloys of tin and lead are used instead of ostensibly pure tin. Thus the so-called rose tin (Bohemian tin) is said to contain as much as 10 per cent. of lead. The presence of arsenic in the tin is said to increase the action of the above kinds of food upon the metal.

Stannous and stannic chlorides, which are used in the arts, produce very violent symptoms of poisoning. These symptoms are those of a toxic gastro-enteritis. In one case one-half a teaspoonful of the substance proved fatal in three days, after very violent symptoms. At the autopsy the same appearances were seen as in corrosive sublimate poisoning.

This substance does not act specially as a corrosive. According to experiments upon animals (Orfila), it produces convulsions and also paralysis.

Tin is eliminated with the urine.

e. Poisoning by Subnitrate of Bismuth.

A few cases of so-called subnitrate of bismuth poisoning may be found in toxicological literature ; even fatal cases have been described. The doses used were from one to two and a half drachms. It is probable, however, that these were cases of arsenic-poisoning, since this is a very common impurity in the officinal preparation of bismuth.

In some of the preparations the normal salt, which is much more soluble, and, therefore, much more dangerous, is said to exist ; also free nitric acid, even in dangerous amount (Husemann).

The existence of a chronic form of bismuth-poisoning is not established.

According to Lebedeff, glycogen disappears from the liver of animals after long-continued feeding with bismuth. The ammonio-citrate of bismuth is said by Stefanowitsch to be a very powerful poison, and to act in a similar manner to phosphorus.

f. Poisoning by Compounds of Gold.

The terchloride of gold only requires mention; this is a powerful irritant and escharotic, like the nitrate of silver.

In addition to this compound, the double chloride of sodium and gold, which produces the same effects, only in a less degree, has come into use again. Gold is eliminated with the urine, and is said to possess a constitutional action which is as yet undetermined. Formerly cases of poisoning have been ascribed to the therapeutic use of this and other preparations of gold.

g. Poisoning by Thallium.

This substance is, as it appears, a powerful poison both in the metallic form and in combination ; the carbonate is said to be fatal to dogs and rabbits in doses of fifteen grains when taken by the mouth, and to rabbits in doses of three quarters of a grain when given subcutaneously. It is, according to Marmé and Rabuteau, a muscular and cardiac poison, and in its action resembles mercury in one respect and potassium in another.

I shall not treat of the compounds of platinum, palladium, osmium, iridium, rhodium, nickel, and cobalt, since they have not yet become important practically, nor has their physiological action been determined accurately. The perosmic acid may be mentioned as having recently attracted the attention of anatomists. Its pungent fumes, like those of iodine, bromine, etc., are very irritating to the mucous membrane of the air-passages; taken internally it is only dangerous in large doses, such as thirty grains and more. Vulpian and Raymond[1] have described one case of osmic acid poisoning in a factory employee.

CHAPTER VIII.

PHOSPHORUS-POISONING.

v. Hauff, Würtemberg. Correspondenzblatt für Aerzte. 1860.—*Lewin*, Virchow's Archiv. Bd. XXI.—*Wagner*, Archiv f. Heilkunde. 1862.—*Mannkopff*, Wiener medicinische Wochenschrift. 1863.—*Ehrle*, Charakteristik d. acuten Phosphorvergiftung. Tübinger Inauguraldissertation. 1861. und Deutsche Klinik. 1861. —*Bauer*, Zeitschrift für Biologie. Bd. VII.—*Eulenburg* und *Landois*, D. Archiv f. klinische Medicin. Bd. III.—*Juergensen*, Berl. klin. Wochenschrift. 1871. —*Nobiling*, Bayr. ärztl. Intelligenzblatt.—*Herrmann* und *Brunner*, Pflueger's Archiv. Bd. III.—*Ménard*, Études expériment. etc. Thèse, Strassbourg. 1869.—*Knoevenagel* (*Traube*), Berliner klin. Wochenschrift. 1869.—*Ebstein*, Archiv d. Heilkunde. 1867 u. 1868.—*Bellini*, Lo Sperimentale. 1867.—*Lebert* et *Wyss*, Archives génér. 1868.—*Cunier* et *Vigier*, Bull. génér. thérapeut. 1868.—*Ranvier*, Gazette médic. de Paris.—*Alter* (*Wyss*), Experimentelle Beiträge u. s. w. Inauguraldissert. Breslau. 1867.—*Bernhardt*, Virch. Archiv. Bd. XXXIX.—*Hartmann* (*Buchheim*), Zur acuten Phosphorvergiftung. Dorpat. 1866.—*Munk* und *Leyden*, D. acute Phosphorvergiftung. Berlin. 1865.—*Th. Husemann* und *Marmé*, Nachrichten d. Geselischaft u. s. w. zu Göttingen. 1866.—*Dybkowski*, Hoppe-Seyler medic. chem. Untersuchungen. Heft. 1.—*Bamberger*, Würzburg. medic. Zeitschrift. Bd. VII.—*Gunning*, Tjidschrift vor Geneeskunde. 1866. (Canstatt Jahresbericht.)—*Klebs*, Virchow's Archiv. Bd. 33.—*Wyss*, Schweizerische Zeitschrift. 1864.—*Schultzen* und *Riess*, Charité-Annalen. Bd. 15.—*Tuengel*, Klin. Mittheilung aus dem allg. Krankenhause in Hamburg. 1863. und Virchow's Archiv. Bd. XXX.—*Vohl*, Berl. klin. Wochenschrift. 1865.—*Schultzen*, Zeitschrift für Chemie v. Beilstein. 1867.—*Koehler*, Ueber Werth und Bedeu-

[1] Gazette méd. de Paris. 1874.

tung des sauerstoffhaltigen Terpenthinöl u. s. w. Halle. 1872.—*Personne*, Comptes rend. 1869. und Bull. génér. thérapeut. 1869.—*Andant*, Bull. génér. thérap. 1868.—*Perls*, Medic. Centralblatt. 1873.—*Wegener*, Virchow's Archiv. Bd. XL.—*Bibra* und *Geist*, Die Krankheiten u. s. w. Erlangen. 1847.

Of phosphorus and its compounds as sources of poisoning, the former only requires notice. Phosphide of zinc has been observed to act in a similar manner. In addition to these, phosphuretted hydrogen is the only compound which has an important poisonous action, which is, however, very different from that of phosphorus, and has never, as it appears, caused poisoning in man. Phosphoric acid, with the exception of a slight irritant effect, has no poisonous action, and the same is true of phosphorous acid. These are practically unimportant.

Of the allotropic modifications of phosphorus only the so-called white phosphorus is poisonous; the red (amorphous) variety is perfectly harmless, even in very large doses.

The detection of white phosphorus is best accomplished by the combined methods of Mitscherlich and Lipowitz. The suspected fluids or tissues, finely divided and treated with water, are placed in a flask connected with an upright glass condenser, and heated over a water-bath in a dark room; if phosphorus is present, luminous vapors will appear in the lower part of the condenser. For further demonstration it is best to introduce into the fluid a few pieces of sulphur (melted on a thread), and first heat out of contact with the air, by closing the condenser; after twenty or thirty minutes the pieces of sulphur on the thread are removed and the condenser opened, when the phosphorescence can be seen upon the entrance of atmospheric air.

If phosphorus was present, a part of it has been precipitated on the pieces of sulphur, and these can be used for other tests.

Phosphorus-poisoning shows itself in two distinct forms, which are sharply defined clinically and in the main anatomically. These are:

Acute poisoning, which has almost invariably been produced by taking phosphorus internally, and chronic, which is caused by the inhalation of phosphorus vapors.

1. Acute Phosphorus-Poisoning.

Phosphorus may be swallowed in five forms: in that of matches, phosphorus pastes (rat poison), more rarely as phosphorus oil, phosphoric ether, and as pure phosphorus. In by far the majority of cases, even with suicidal intent, it is taken in the form of matches. The frequency with which this is used for suicidal purposes has increased enormously during the last ten years, although recently its use appears to be decreasing somewhat. Hundreds of cases can easily be found in literature. Matches are also the frequent source of criminal poisoning, and in children only of accidental poisoning. Phosphorus pastes have frequently been used with criminal and suicidal intent, and have also been taken accidentally. Pure phosphorus, phosphorus oil, and phosphoric ether are difficult for the laity to obtain; these are often the cause of medicinal poisoning. In England a patent medicine for the treatment of worms was found to contain a large amount of phosphorus. This preparation gave rise to one fatal case of poisoning.

The local action of the phosphorus upon the stomach is materially less when it is taken in large pieces than when in a finely divided state. The so-called fire-eaters are said to swallow whole sticks of phosphorus, weighing fifteen grains and more, without injury. Van Hasselt doubts this statement; in favor of it, however, is the fact that, in animals, very large pieces pass from the intestine almost unchanged, and have but slight action. Whenever phosphorus has produced severe poisoning, it has almost always been used in a finely divided state or dissolved (in oil or ether). In such a condition it is a very active poison; for an adult, one grain should be designated as a dangerous or fatal dose; for children, a small fraction is sufficient. The amount of phosphorus in matches varies exceedingly (according to Gunning, from one-fifth to one grain in one hundred match-heads). Moreover, their action varies according as the heads are swallowed whole, or an extract or emulsion prepared with water, alcohol, or some fatty fluid, like milk, which dissolves phosphorus more easily, is taken; notice should also be taken of the manner

in which the phosphorus paste is applied to the match; whether, for example, the head is soaked or coated with a varnish which is difficultly soluble in water or not. An important factor in determining this is the rapid appearance or absence of vomiting.

Thus it can be easily understood that in one case severe poisoning has been observed after taking 35 or 40, and even after taking 8 matches (in a child two years old), while in another even 400 matches did not prove fatal. The amount of phosphorus in pastes used for poisoning rats varies greatly, according as the paste is freshly prepared or not.

The case of Harting, in which the ingestion of a single match is said to have produced severe poisoning, is open to considerable doubt.

It may be stated here that no authentic case is known in which poisoning has been caused by the burning of matches; the experiments performed by van Hasselt and Pappenheim to settle this question, so often discussed by the laity, gave only negative results. Non-susceptibility to the action of this poison, acquired by habitual use, or so-called idiosyncrasy, does not exist; most animals, also, are affected by it to about the same extent as man; parrots only are said to enjoy immunity.

Symptoms.

The first symptoms of poisoning are usually gastric: pain in the epigastrium and vomiting; the latter is usually not violent, occurring but once, or only a few times. Generally it comes on in the course of the first twenty-four hours, frequently soon after the ingestion of the poison. The vomited matters, except when they contain phosphorus, show nothing special. When phosphorus is present they are luminous in the dark. Discharge of luminous masses *per anum* has been observed; occasionally, when much phosphorus has been taken, a luminosity of the breath has been noticed soon after the ingestion, but it is probable that in these cases the luminous gas came from the mouth or stomach, and not from the lungs. Frequently the peculiar odor of phosphorus is perceptible in the breath. Other symptoms do not necessarily follow the vomiting, if the stomach has been com-

pletely emptied, or if the dose has been small. Almost always, however, there comes on a comparatively healthy condition, which may last two or three days, or even longer. Then the severe symptoms begin usually with jaundice, which increases more or less rapidly until it reaches the highest degree of intensity; with this comes urticaria, which generally accompanies severe jaundice. Simultaneously with the icterus there is more or less pain in the epigastrium, especially in the region of the liver. At this time enlargement of the liver can usually be detected by palpation and percussion, and this organ continues to increase while the patient is under observation; mild febrile disturbances are frequent, and vomiting, now more or less bloody, comes on again. With the appearance of these symptoms there is very great disturbance of the general condition, and soon alarming weakness of the heart's action is noticeable. The pulse varies greatly in frequency (in one case the number of pulsations was diminished to 40), being much accelerated, extremely feeble and small toward death; the heart-sounds are feeble, and are early characterized by the failure of any difference between the first and second sounds (fœtal heart-sounds — Stokes); finally, the first sound disappears entirely.

At the height of the disease there is frequently a tendency to hemorrhage of various kinds; the vomiting of blood above mentioned may be very copious, and with it there may be bloody stools; also bleeding at the nose, metrorrhagia, and often premature appearance of the menses. The hemorrhage into the skin and subcutaneous cellular tissue shows itself in the form of petechiæ and extensive ecchymoses. The hemorrhage from a simple leech-bite or from cupping cannot be stopped.

The intellect sometimes remains entirely intact; profound stupor is a bad symptom; it precedes death by not more than twenty-four hours. The failure of the intellect may show itself in different ways: as simple coma, as coma with restlessness, and in some cases as violent, noisy delirium. Convulsions are not rare as death approaches. The temperature of the body remains about normal until the approach of death. Then, for the first time, there is a lowering of the temperature, or in some cases a considerable increase.

Of especial interest is the character of the urine eliminated. At first there is no marked change in amount or density; later it is diminished in amount, during the last few days even to the minimum (between three and four ounces). It usually contains a small, rarely a large, amount of albumen, frequently blood and so-called fibrinous casts, and, with the appearance of jaundice, biliary pigments and acids. Leucin and tyrosin are rarely found in it, but paralactic acid is often detected in large amount, especially in fatal cases. Schultzen and Riess found that the urea almost completely disappeared upon the approach of death; and in its stead there appeared, even in cases ending in recovery, a peculiar nitrogenous "extractive" material, which was, according to these authors, very similar to peptone. In experiments upon animals, this disappearance of urea could not be produced.

Death may take place unexpectedly at any time, even before the appearance of the most unfavorable symptoms, and frequently toward the end of the first week, or sometimes in the second week. Slightly marked gastric symptoms by no means authorize the prediction of a mild course of the poisoning. In cases of recovery from severe poisoning, the disease may drag along for a long time. In the cases of this kind observed by Schultzen and others, the swelling of the liver did not disappear for more than four weeks; the jaundice disappeared, albumen could no longer be detected in the urine, and the repeated and copious intestinal hemorrhage ceased.

A very different form of poisoning from that above described is one in which the progress is very rapid; this occurs in very acute poisoning. In one case death took place in less than nine hours, and cases which have proved fatal in two or three days are not rare. In such cases all of the symptoms develop much more quickly. The vomiting which first appears may be followed immediately by the most severe symptoms.

Jaundice is only absent in those cases which run a very rapid course; in one case (Drachmann), however, it did not appear, although death did not take place until the fourth day.

In a very few cases an apparent diminution in the size of the liver, which was previously enlarged, has been observed a few days before death.

Post-mortem Appearances.

The great interest which phosphorus-poisoning has won for pathology, during the last decade, depends in great measure upon the pathological appearances to which it leads. In this connection v. Hauff has performed the greatest service, by teaching that fatty degeneration of the liver is a usual result of this form of poisoning. After death there is found, almost without exception, a more or less intense yellow coloration of the skin and conjunctivæ (compare that which relates to icterus under "Symptoms"). Ecchymoses or petechiæ are also frequently seen. The muscular tissue is usually yellowish-red and fatty. On opening the abdomen, the familiar garlicky odor of substances containing phosphorus is perceived. The blood is only partly coagulated. Ecchymoses are seen beneath the pericardium and endocardium. The muscular tissue of the heart is pale, and evenly colored of a light grayish-yellow, or in some cases (especially apparent beneath the endocardium) it is striped or contains net-like tracings formed by light wavy lines upon a grayish-red ground; the cardiac tissue is brittle, and appears fatty both to the touch and to the eye; in short, we see a typical fatty heart. The lungs show nothing abnormal, except the hypostatic congestion, and the pleural and bronchial ecchymoses. The liver is, as a rule, enormously enlarged, and presents the appearance of one in a high degree of fatty degeneration; it is usually pale-yellow, but may be deep-yellow; the acini are plainly perceptible and large. The substance is brittle and fatty; here and there ecchymoses beneath the capsule or along the course of the blood-vessels may be seen. The spleen is often recently enlarged. The gastric mucous membrane is swollen, grayish, and non-transparent, with small or large ecchymotic spots, and rarely ulcers, which are small and in the pyloric region. The mucous membrane of the duodenum often presents the same appearances. That of the small and large intestine is pale, with occasional ecchymoses. The contents of the stomach and intestine are often bloody; the intestine contains but little or no bile, and the gall-bladder but little of a biliary or rather mucous fluid. The kidneys are very much enlarged and fatty.

In the central nervous system there are no important changes.

In a few cases, in which the duration of the disease was only a few hours, the autopsy gave almost completely negative results. Sometimes important changes occur only in the liver. In many cases this organ is scarcely enlarged, and may be even diminished in size. It no longer has so pale a yellow color, but is, on the whole, more of a dark-red; its consistency is tougher; the lobules are small and wasted. In this dark-red tissue may be seen occasionally insulated spots of varying size, which have the ordinary appearance of phosphorus-poisoning, and are of a strongly-marked yellow color. Under such circumstances the appearance of the liver gives the impression that the fatty degeneration, which in the yellow patches is still in its prime, has in the red portions advanced to the stage of atrophy.

Microscopic examination shows, as the cause of the fatty appearance of the organs, that the muscular fibres of the heart and muscles of the body, the hepatic and renal epithelial cells, and the cells of the gastric glands, are filled with large or small fat drops. Klebs found also fatty degeneration of the smaller blood-vessels and capillaries, to which he attributes the hemorrhages.

The reports and opinions of authors differ in regard to the appearances in the liver. Some of the authorities, at the head of whom stands Mannkopf, found, especially in those cases with commencing atrophy, proliferation of cells in the interstitial tissue, an increase of this tissue, and aggregations of nuclei; others, among whom are Schultzen and Riess, never have seen such an active process in the interstitial tissue, but simply a fatty degeneration of the cells. This difference in the microscopic results has importance in connection with the controversy as to whether the changes taking place in the liver in phosphorus-poisoning are essentially different from those in acute yellow atrophy of the liver or not.

The experiments of Wegener are conclusive so far as the anatomical side of the question is concerned.

Wegener found "an interstitial hepatitis of the most marked degree. The result of this, when produced by the use of relatively large doses of phosphorus continued for several months (that is, in comparison with the doses used by Wege-

ner to produce a modification of the growth of bone, such as, for example, 0.0015 gramme (one-fiftieth of a grain) in rabbits, is always essentially the same, namely, an atrophy of three kinds: smooth induration of the organ, or a form of atrophy occasionally seen in man as the result of syphilis, a hepar lobatum with numerous deep contractions which produce a great deformity of the organ, or, finally, the typical granular atrophy, the classical cirrhosis of the liver. In all of these cases chronic icterus is present. If the atrophy is of the last-mentioned variety, there are found those regularly developed secondary affections, which are familiar in human pathology, viz., venous hyperæmia of the stomach and intestines, indurative enlargement of the spleen," etc.

This complete description leaves no doubt about the fact that in cases of chronic poisoning by phosphorus the most exquisite proliferation of cells takes place in the interstitial tissue of the liver; this gives, therefore, the most important evidence in favor of the views of those who, with Mannkopf, consider the changes which take place in the liver in acute phosphorus-poisoning and acute atrophy of the liver as identical. The chemical side of this question must be considered later in the theoretical part.

In cases of very acute poisoning, in which the post-mortem examination has not been postponed too long, phosphorus can frequently be detected in the contents of the stomach and intestines by its luminosity in the dark, or by means of Mitscherlich's apparatus; in other cases the detection of phosphorous acid renders it at least probable (Sonnenschein) that white phosphorus was present.

Tuengel, by means of Mitscherlich's process, detected phosphorus in the liver of a girl who died nine hours after swallowing matches, the autopsy having been performed forty hours after death.

On the contrary, in one case, in which death took place within twenty-four hours after the poisoning, phosphorus could not be detected in any organ.

Theoretical and Experimental Considerations.

Of the theoretical questions bearing on acute phosphorus-poisoning the one most discussed is, whether the disease is due to the direct action of the phosphorus on the metamorphosis of tis-

sue, or to that of some compound of phosphorus formed within the system.

Phosphorous and phosphoric acids may exist in the body as the result of the oxidation of the poison; the facts which lead to the assumption that these compounds are products of intermediate steps in its action are not conclusive. Moreover, the injurious action of these compounds is far too slight in proportion to the powerful action of free phosphorus.

One of the principal reasons given by some of the investigators of the present day for considering that phosphorus could not act as such in the blood and tissues was its supposed insolubility in water, in the stomach, and in the blood.

Phosphorus is, however, as Buchheim and Hartmann have demonstrated, soluble in water at a temperature of from 96.8° to 104° Fahr., in the proportion of 0.022 per cent.; but in the organic fluids, such as the bile, it is somewhat more soluble. It is also true that phosphorus, when taken into the body—especially into the stomach—either in solution or undissolved, goes into the blood. This has been proved both in cases of poisoning in man, and experimentally by poisoning animals. Luminosity of the breath has been observed in animals when the phosphorus has been introduced into the stomach through the œsophagus, after œsophagotomy had been performed and the œsophagus tied above the wound. In one case, after exposure to phosphorus vapor, Vauquelin observed distinct luminosity of the urine.

The objections, therefore, against the supposition of a direct influence of the phosphorus upon tissue-metamorphosis are untenable.

A second question still undecided is, In what way is this action of phosphorus to be regarded? It has been thought that the phosphorus, or phosphuretted hydrogen formed from it, acts simply as a deoxidizer, but the poisonous doses are much too small to accomplish this.

Schultzen almost always found paralactic acid in the urine in fatal cases of phosphorus-poisoning. Schultzen and Riess found, in the earlier stages of poisoning, a peptone-like substance; Wyss found leucin and tyrosin; Schultzen and Riess detected tyrosin in the blood of dogs poisoned with phosphorus. These

authors saw the urea — the principal product of normal tissue-metamorphosis—almost entirely disappear from the urine in fatal cases. Since it has been well established that lactic acid is, under normal conditions, oxidized, the view of Schultzen and Riess, that the presence of phosphorus in the organism interferes with the process of oxidation, is probably correct. The appearance of leucin and tyrosin and all of the other intermediate products of metamorphosis (the so-called peptones) in the urine corresponds entirely with this view. How this action is to be explained is completely unknown.

In this, as in all other cases, the almost constant appearance of jaundice depends upon the reabsorption of the bile ; the simultaneous presence of a large amount of the biliary acids in the urine proves this, as in many such cases of icterus an obstruction to the flow of bile cannot be detected.

The hemorrhages appear to depend upon the fatty degeneration of the walls of the smaller blood-vessels.

The symptoms of gastro-enteritis depend, in small part only, upon the local irritation ; perhaps the products of the oxidation of the phosphorus (phosphorous and phosphoric acids) may take part in this action ; in general, these symptoms, especially so far as they belong to the later periods, are consequences of the general action. The constant changes in the mucous membrane of the stomach, the gastro-adenitis of Virchow, are of the same nature as the changes in the liver, muscles, and kidneys ; these are found also after the injection of phosphorus oil into the rectum. Whether the fatty condition of all of these organs is to be regarded as a simple fatty infiltration—that is, a deposition of fat owing to its non-consumption—is not decided. The considerable increase of fat in the blood appears to favor this view (Méhu). Méhu found three per cent. of fat in the blood of dogs poisoned with phosphorus, against two per cent. under normal conditions. Bamberger, on the contrary, found no increase of fat in the blood. The fact that in the liver, where this fatty condition is most marked, genuine inflammatory (interstitial) changes may exist somewhat contradicts this view.

Perls has, as it seems, given the proper definition to distinguish between fatty infiltration and fatty degeneration. If, in a

tissue, fat is stored up, and there is a diminution in the amount of water and a corresponding increase of the non-volatile constituents, this may be considered as a fatty infiltration. Fatty degeneration exists where, with a tolerably constant amount of water, the fat takes the place of other non-volatile substances.

In the livers of two dogs poisoned with phosphorus I found:

	At a temperature of 212° Fahr.	
In 100 grammes of liver.	25.78 of dried substance.	12.5 of fat.
	24.2 " "	8.0 "

In dogs, under normal conditions, I found that the amount of water never exceeded 75 per cent.; the above figures, therefore, show that the fatty condition of the liver, at any rate, in phosphorus-poisoning, is due to fatty degeneration. Bauer's estimations of fat in the livers of dogs poisoned with phosphorus and his conclusions from other considerations, agree with this.

Practically, as well as scientifically, the question as to the identity of the changes in acute phosphorus-poisoning and acute atrophy of the liver, is interesting. The anatomical side of the question has been already treated in speaking of the post-mortem appearances; the changes in tissue-metamorphosis, however, in no way appear to be the same in the two cases. The most important labors of Schultzen and Riess in regard to the chemistry of these changes lead to the conclusion that the very frequent appearance of sarkolactic acid in the urine is characteristic of the changes in tissue-metamorphosis in phosphorus-poisoning. Since this substance has thus far never been found in acute atrophy of the liver, we may accept this conclusion. Less characteristic is the appearance of leucin and tyrosin in acute atrophy of the liver, since these substances have been repeatedly detected in the urine in phosphorus-poisoning, although in much smaller amounts than in acute atrophy of the liver (Wyss).

Finally, although no more essential differences can be established in the processes taking place in acute atrophy of the liver and acute phosphorus-poisoning, yet it cannot be concluded that idiopathic acute atrophy of the liver does not exist, and that in doubtful cases phosphorus-poisoning must be inferred. This

unwarranted conclusion would lead to very dangerous consequences, especially in medico-legal practice.

Treatment of Phosphorus-Poisoning.

This must aim exclusively to render the poison harmless before its absorption into the blood. This is best accomplished, if the patient is seen early enough—that is, at the latest within the first twenty-four hours,—by the administration of emetics, or better still by the use of the stomach-pump in combination with active cathartics. The physician can always do this, if he has an œsophageal sound. Bamberger considers sulphate of copper to be the best emetic. By the use of this drug we succeed in producing, in addition to the act of vomiting, an at least temporary harmlessness of the poison ingested. The copper salt forms with the phosphorus a compound which is very slightly soluble, so that the pieces of phosphorus in the stomach (heads of matches, etc.) are surrounded with a coating of the slightly soluble phosphide of copper.

Recently oil of turpentine has been recommended as an energetic antidote in acute phosphorus-poisoning.

The use of oil of turpentine in chronic phosphorus-poisoning (by the vapor) is old; it is based upon the fact that the vapor of phosphorus is not luminous in an atmosphere strongly impregnated with turpentine. Andant introduced the use of turpentine into the treatment of acute phosphorus-poisoning. According to Koehler, no action takes place except with the unrectified oil of turpentine. The greatest scepticism should be placed against the wide-spread enthusiasm of some advocates of this treatment, as Bamberger has already indicated. We must insist that, notwithstanding the numerous records concerning this so-called antidote, it is not proved that its action is absolutely certain. The cases observed are not sufficiently conclusive, and the results of experiments are not entirely in harmony. Moreover, the antidote acts with certainty only when the amount of phosphorus taken does not much exceed the ordinary fatal dose; it is without effect when the dose is very large. But the action of a dose ordinarily fatal is often uncertain when no antidote is

given, the effect frequently being much less than would be expected.

It is not, therefore, just to assert that the timely administration (within twenty-four hours) of oil of turpentine renders it unnecessary to remove the poison by evacuating the stomach. The latter is by far the more important. Nevertheless, turpentine is doubtless to be recommended, and can be borne in doses of thirty minims and more every fifteen minutes until a total of two fluid drachms and a half and upwards is reached.

The antidotes formerly recommended have not stood the test. The same is true of the administration of albumen, etc., to envelop the poison. All fatty substances, and also the yolk of eggs, are to be studiously avoided on account of the ready solubility of phosphorus in fat. Transfusion has naturally been recommended by Eulenburg and Landois in acute phosphorus-poisoning, but satisfactory experiments as to its results have not been reported.

It is out of place here to treat of the rules which have been or should be adopted by boards of health to diminish the occurrence of phosphorus-poisoning. These could refer only to phosphorus pastes so frequently used for poisoning rats, and to matches. The pastes seem to possess such advantages for the destruction of these pests, that it is difficult to do without them. In the manufacture of matches, the aim appears to have been, almost from the beginning, to replace the dangerous white phosphorus by the innocuous red variety. When the so-called Swedish matches, which contain no phosphorus, shall come into general use, an absolute prohibition from employing the latter in the manufacture of the inflammable part of matches may be seriously considered. This would at the same time do away with the most important source of chronic phosphorus-poisoning.

2. Chronic Phosphorus-Poisoning.

Of the forms of chronic poisoning, that caused by the inhalation of phosphorus vapor is the only one which has been established with certainty and is well recognized. Such cases seem to occur very rarely in the phosphorus factories; but they are,

on the contrary, frequently observed in workers in match factories. Those workmen who are engaged in dipping the wood into the phosphorus mass, and those employed in the drying-rooms are the principal ones who are liable to be poisoned. This form has also been observed in the so-called phosphorus bronze factories.

As symptoms of chronic phosphorus-poisoning are mentioned: chronic bronchial catarrh, accompanied by chronic gastro-enteritis, loss of appetite, and usually constipation. The most important and only specific result of the poisoning is the familiar disease of the lower jaw, called phosphorus necrosis.

This develops in from six months to many years after the workman has commenced the dangerous employment; occasionally the first symptoms are not observed until after the patient has ceased working with phosphorus. The disease occurs in the lower jaw most frequently and most severely; in the upper jaw rarely and in a milder form. Yet the most extensive necrosis of the upper jaw has been observed; even cases are known in which the disease has extended to the cranial bones, and death from meningitis has followed.

The disease almost always begins in carious teeth or gaps between the teeth, and almost never exists in persons with sound teeth. It develops into and runs the course of a chronic periostitis, and leads to extensive necrosis of the lower jaw. In the milder cases the disease is limited to the alveolar process; then, after the spontaneous expulsion or the extraction of the necrosed portions, recovery takes place; in the severe cases necrosis of the greater part or the whole of the jaw results, yet recovery may ensue even in these cases.

The occurrence of abundant osteophyte formations on the affected bones has long been recognized as the anatomical peculiarity of the disease.

The frequency of similar diseases seems to have diminished considerably in recent times.

Sufficient ventilation is the most important precaution for the protection of the workmen; in many factories only workmen with perfectly sound teeth are employed.

The treatise of Wegener is absolutely necessary for the thorough understanding of this subject.

Wegener showed that it is easy to produce in animals the peculiar periostitis of the lower jaw, which leads to necrosis, by exposing them for several weeks to the action of phosphorus vapor. This evidently acts as a local irritant upon the periosteum, acting more readily in those cases where opportunity is given for the attack of the vapor by decayed or previously wounded teeth.

Wegener showed also that phosphorus taken in the form of vapor by inhalation or internally, in the smallest doses, acts "as a specific formative excitant to the osteogenic tissue," and under otherwise normal conditions leads to a considerably increased development of the compact tissue in the long bones. These results are shown most plainly in young animals while still growing; in them it happens that not rarely all of the spongy tissue is crowded out and its place filled with compact tissue. Wegener has succeeded in producing in hens a complete closure of the medullary cavity by compact bone tissue.

CHAPTER IX.

POISONING BY ARSENIC AND ARSENIURETTED HYDROGEN.

Fleck, Archiv für Biologie. Bd. VIII.—*Boehm* und *Johannsohn*, Arch. für experimentelle Pathologie. Bd. II.—*Lehmann*, Het-Arsenikzuur. u. s. w. Dissertat. Amsterdam, 1773.—*Cunze*, Henle und Pfeufer's Zeitschrift. III. Bd. 28.—*Schaper*, Beiträge zur Arsenikvergiftung. Berlin, 1846.—Diskussion zwischen *Schaper* und *Pfeufer* in Henle-Pfeufer Zeitschrift. I. Bd. 6.—*Schmidt* und *Stuerzwage*, Moleschott Untersuchungen. Bd. VI.—*Boehm* und *Schaefer*, Würzburger Verhandlungen. N. F. III.—*Saikowski*, Virchow's Archiv. Bd. XXXIV.—*Schaefer*, Sitzungsber. der Wiener Akademie. Math. naturwissenschaftl. Classe. Bd. 41.—*Virchow*, Dessen Archiv. LVII.—*Sklarek*, Reichert u. Dubois Archiv. 1866.—*Grohe* u. *Mosler*, Virchow's Archiv. Bd. XXXIV.—*Mueller*, Wiener medic. Wochenschrift. 1866.

Arseniuretted Hydrogen:—*Vogel*, in Neubauer und Vogel's Anleitung u. s. w. Wiesbaden, 1863.—*Naunyn*, Reichert und Dubois Archiv. 1868.—*Eulenberg*, Die schädlichen u. s. w. Gase.

The detection of arsenic in the animal fluids and tissues is only possible, as in the case of the other poisonous metals, after

previous destruction of the organic matter by hydrochloric acid and potassic chlorate; incineration of the substances to be analyzed is not permissible, since the terchloride of arsenic, which is formed by compounds of arsenic in the presence of the alkaline chlorides, is quite volatile. For the same reason also the destruction of the organic matter with hydrochloric acid and potassic chlorate must be performed over a water-bath. From the solution thus obtained the arsenic is precipitated in the form of sulphide, and this compound, after purification and, as a rule, conversion into arsenic acid, is used for obtaining the characteristic reactions.

The best process for finally determining whether a suspected substance is or contains an arsenical compound is that of Marsh. When articles which may serve as the source of poisoning, such as wall-paper, colored clothing, food, etc., are to be tested for arsenic, Marsh's test can be performed directly with the suspected material. In the examination of articles of food and also of vomited matters in cases of suspected poisoning, it is well to remember that the arsenic is usually employed in the form of arsenious oxide. This is mixed with the substance usually only in a coarsely powdered state, and is, moreover, soluble with difficulty; on this account, and also on account of its high specific gravity, it is frequently possible, after allowing the mixture to settle, carefully decanting and washing the sediment, to find at the bottom of the vessel particles of the arsenious oxide, with which the arsenic mirror can be obtained immediately by Marsh's test or by reduction with charcoal.

The quantitative estimation is made by obtaining the ammonio-magnesian arseniate in a pure form. A very complete description of all the methods and manipulations used in the detection of arsenic may be found in Otto's Anleitung zur Ausmittelung der Gifte, Braunschweig, 1856.

Acute and chronic arsenic poisoning are totally different in nature and importance.

Acute poisoning by arsenic has been and is at the present time by far the most frequent cause of death by poisoning. In the different European countries, at the present time, more than three-fourths of all the cases of poisoning or attempted poison-

ing which have been investigated legally are due to the compounds of arsenic. The inventor of the famous aqua toffana (which according to Garelli was nothing more than a solution of arsenious acid in aqua Cymbalariæ) confessed that he knew of 600 cases of fatal poisoning caused by this preparation alone.

Of the compounds of arsenic, arsenious oxide (so-called white arsenic) is almost exclusively used. The other compounds have but little importance. According to the latest investigations of Schroff upon this subject, metallic arsenic, whose poisonous properties were formerly denied by C. Schmidt, is almost as active as arsenious acid. At all events, the so-called fly-powder, which is a frequent source of accidental and criminal poisoning, and which consists chiefly of metallic arsenic, is by no means harmless. This may, however, act by virtue of the arsenious oxide, which is always mixed with it in amounts varying from ten to thirty per cent. Arsenic oxide, which is almost as active as the arsenious, practically is not employed as a poison.

The pure sulphides of arsenic are not poisonous, although the native sulphides found in commerce and also the artificial preparations (orpiment, King's yellow, realgar, etc.) always contain mechanically mixed with them considerable amounts, even to thirty per cent., of arsenic acid.

The salts of arsenious and arsenic acids act, as a rule, more powerfully than the acids themselves, since the latter are much less soluble.

Among the most important compounds of arsenic are the arsenical pigments, especially the so-called Schweinfurt green (a mixture of the arsenite and acetate of copper) and Scheele's green (arsenite of copper). The organic compounds of arsenic (kakodyl, for example) and arseniuretted hydrogen have a special pathological action which will be spoken of later.

The methods by which the poison may get into the body are very different. The ingestion of arsenic in food or drink, with which it has been intentionally or accidentally mixed, may easily take place unnoticed even in very large amounts, since the various preparations in small quantities are tasteless; by far the largest number of cases of severe acute poisoning are caused in this way. Cases of acute poisoning have also been observed due

to the illegal use of arsenical preparations (pigments) for coloring playthings of children, who have sucked them. Rarely such cases occur due to the dust of arsenical colors, such as from the green tarlatan dresses which have been colored with Schweinfurt green. The external application of arsenious oxide or of orpiment even upon the normal skin for depilation has caused severe acute poisoning. The very frequent use, especially in patent medicines, of arsenical ointments and lotions for benign and malignant ulcers has resulted in several fatal cases of poisoning.

The amount of arsenic which is sufficient to produce acute poisoning has been determined by many observations. Doses of less than one-sixth of a grain have produced injurious effects in adults. Evident symptoms of poisoning have been observed as the result of taking from one-fourth to one-half of a grain. In one case alarming symptoms were produced in a female by the continued use during four days of one-twenty-second of a grain daily. Such serious symptoms were produced in two men by taking a little less than two grains, dissolved in wine, that Taylor does not hesitate to ascribe an occasional fatal result to such a dose. The correctness of this view is established by an observation also made by him: a woman took half an ounce of Fowler's solution, which contains not quite two grains of arsenious oxide (as potassic arsenite), in unknown doses during five days with a fatal result, and a strong servant-girl was killed by about two grains of arsenious oxide in two ounces of fly-water in thirty-six hours.

The fatal dose does not seem to be very much smaller for children.

On the other hand, cases are well known (leaving out of account entirely cases of arsenic-eaters, which will be spoken of later) which show that arsenic sometimes does not prove fatal, even in doses of more than from fifteen grains to two ounces.

Some of the conditions upon which the variation in intensity with which the poison acts in different cases are well known. It acts more severely when in solution than when undissolved; hence, in general, the action of the very soluble alkaline arsenites is more powerful than that of a corresponding amount of the free acid. In this respect a distinction must also be made between

the two modifications in which arsenious oxide exists. The non-transparent variety is very slightly soluble in cold water, that is, in from 500 to 1,000 parts, and in 400 parts of boiling water; after boiling an hour it is, according to Taylor, soluble in forty parts; by longer boiling with water the opaque variety is changed to the vitreous, of which boiling water dissolves about one part in ten.

Moreover, the poison acts much more violently when taken upon an empty stomach. The so-called cumulative action does not exist, on account of its very speedy elimination with the urine. The experience of habitual arsenic-eaters goes to show that, in the case of this poison, habit affords a tolerably good protection against its action.

Symptoms of Acute Arsenic-Poisoning.

The symptoms appear much more quickly after large doses and when taken in solution. They rarely come on later than one hour after the ingestion, but in exceptional cases they may be delayed for six or eight hours. As a rule, the statement, frequently made, that there is a special taste upon the ingestion of the poison or as a beginning of the poisoning, is erroneous; the taste is usually completely absent or is unimportant. The first symptoms, whether the arsenic is taken internally or applied externally, are those of a very violent gastro-enteritis, which frequently from the beginning runs a course resembling that of cholera: violent vomiting and purging, the discharges often resembling rice water, although sometimes they are bloody; the vomited matters are sometimes colored greenish from admixture with bile. The law in many places orders that arsenic before it is sold shall be mixed with coloring matters, such as charcoal or indigo, which will impart their color to the vomit. Usually there is violent pain in the abdomen. Collapse of dangerous intensity appears very quickly, and consciousness is usually retained till death. In other cases coma and convulsions appear in a longer or shorter time before death. Trismus has also been reported.

The progress of acute arsenic-poisoning is, however, liable to many variations. In the first place, it may be influenced by the

mode of application, as, for example, by the cutaneous eruptions when applied to the skin. Yet cases occasionally occur which run an entirely abnormal course, as, for example, cases in which the gastric symptoms are entirely wanting or but slightly marked, while collapse, which proves rapidly fatal, comes on very suddenly—in twelve hours or even earlier after the poisoning. Such cases appear to occur with relative frequency when the doses are very large. In these cases there is often a severe affection of the nervous centres, as shown by the delirium, coma, and convulsions, occurring especially in the form of an acute eclamptic attack. Paralysis is also not rare. Christison mentions this as the most frequent of the secondary symptoms in arsenic-poisoning. This will be treated in detail under the head of Chronic Poisoning.

The urine is sometimes albuminous or bloody. The perspiration is said to sometimes have an odor like that of arseniuretted hydrogen.

The progress is usually rapid and fatal in more than one-half of the cases. Death generally takes place in from twenty-four hours to four days, but in many cases after a few hours, and sometimes not until after the lapse of two weeks. Remissions, during which the patient is apparently better, often occur during the progress of a case. In cases terminating in recovery there may remain behind many sequelæ, among which may be mentioned especially general emaciation, with ulceration and gangrene of the skin, œdema, anæsthesia, and paralysis (especially of the lower extremities), and frequently also gastralgia, dyspepsia, and chronic intestinal catarrh.

The appearance of the cutaneous eruption in many cases is very peculiar; an eruption like that of eczema and urticaria has been observed after both the internal and external application of the poison. Of course, those eruptions caused by its direct application to the skin are not referred to here.

Post-mortem Appearances.

After death from arsenic-poisoning the stomach presents the most characteristic appearances. The mucous membrane shows

signs of the most intense inflammation ; it usually has a dark-red color, which is distributed in spots or stripes. This color is not the result of simple corrosion, although particles of the poison are occasionally seen adhering to such portions of the mucous membrane, since precisely the same appearances are seen upon the mucous membrane of the stomach after death from the external application of arsenic. This inflammation is sometimes so severe as to produce hemorrhagic exudation or infiltration, which is often quickly followed by death of the tissue and ulceration of the membrane. Ulceration may take place in a few hours ; in three cases, according to Taylor, this led to perforation of the stomach during life. In some cases the signs of intense exudative inflammation are completely absent, as in one case in which Virchow found the appearance of acute parenchymatous gastro-adenitis, as he formerly described it, in connection with phosphorus-poisoning. Besides the above appearances in the stomach there is nothing characteristic in the cadaver ; ecchymoses beneath the endo- and pericardium, and imperfectly coagulated or fluid blood have been mentioned. More recently, since the discovery of fatty degeneration of the liver, etc., as a result of the action of arsenic, a similar condition of fatty and parenchymatous degeneration of the muscular tissue of the heart, of the liver, etc., has been found in the bodies of those who have been poisoned. After arsenic-poisoning bodies do not putrefy, or only very slowly, but become mummified, so to speak. Usually the contents of the stomach and intestine contain the poison in those cases in which life has lasted only a few days at the longest, and if the arsenic was taken in the form of arsenious oxide, it is apparent as small granules, which are seen under the microscope to consist of small octahedral crystals. After a few days, however, or even sooner, especially in cases where violent vomiting and purging have taken place, all of the arsenic may disappear from the contents of the stomach and intestine ; then it is found in the liver and other organs of the body, in which it can be detected very soon after it has been taken, especially if in very large doses. It is said to exist in the bones as calcic arseniate, a compound isomeric with calcic phosphate. After fourteen or fifteen days, however, it disappears from all of the organs. The

elimination takes place in appreciable quantity with the urine and bile.

In forensic cases it is of interest to know that arsenic can be detected in bodies which have been buried many years. Bodies do not absorb arsenic from the earth, even when that of the grave contains it, as it sometimes does. The tissues of the normal human body contain no arsenic. It is extremely improbable, to say the least, that arsenic can be fixed in the tissues of the body in more than the merest trace, after its long-continued ingestion in small amounts, as when administered therapeutically.

The *treatment* under all circumstances is to be directed to emptying the stomach; in most cases, therefore, vomiting should be produced immediately, or the stomach-pump should be used; any emetic is allowable, but it is best, if possible, to avoid using those substances which, like tartar emetic, strongly irritate the mucous membrane of the stomach. To counteract that portion of the arsenic not expelled from the stomach by vomiting, freshly prepared ferric hydrate or magnesia should be given in large amounts, and this treatment should be continued for days after the poisoning. The magnesia acts, at the same time, as a cathartic; otherwise care should be taken to produce abundant evacuations by the administration of cathartics, since if the arsenical compound formed with the antidote be allowed to remain long in the stomach or intestine, it acts as a poison, probably owing to its decomposition, so that the arsenious acid is set free. Moreover, all of the arsenic is never converted into a harmless compound, especially when it has been taken in the solid form, in which case small crystals of undecomposed arsenious oxide are frequently found in the mixture of ferric hydrate or magnesia. Milk, albumen, etc., should be given at first to envelop the poison until the antidote or emetics can be obtained.

In other respects the treatment of gastro-enteritis is to be employed. The dangerous collapse which always occurs indicates early and strong stimulation.

Chronic Arsenic-Poisoning.

The same compounds which cause acute poisoning may also give rise to chronic. The ways in which the poison may get into the body are sufficiently numerous.

In the first place, a mild form of chronic poisoning is not very rare as the result of the therapeutic use of Fowler's solution. It results generally from using the drug continuously for weeks, but it may also come on quickly after taking the ordinary doses.

More important are cases of professional poisoning, to which in its worst form workmen in arsenic mines are especially liable, and also those engaged in smelting ores which contain arsenic, although they are not worked for it; this is the case in smelting many of the copper, lead, and other metallic ores. We also meet with professional poisoning among those who work in anilin colors (fuchsin, etc.) and arsenical pigments (Scheele's and Schweinfurt green, arsenic red, etc.), among furriers, felt-workers, shot-makers, and workers in many metals, who frequently handle arsenic in alloys. Arsenic is also used in large amounts in glass-works for enamelling and decolorizing glass, but cases of poisoning from this source are unknown.

Those poisonings should be termed illegal which are caused by working with cloth, artificial flowers, etc., which are colored with arsenical pigments. Green tarlatan is very frequently colored with arsenical green, also artificial flowers, red and green, although, according to Pappenheim, less frequently. The loose manner in which the pigment is attached, especially to cloth, renders it very easy for the poison to become diffused in the form of dust, and thus to give rise to poisoning in seamstresses and girls engaged in the manufacture of artificial flowers, and also in persons who wear these articles. Many green and red enamelled papers contain arsenic and may do injury, especially when used for wrapping confectionery. Toys are also sometimes painted with arsenical pigments. Red lacquer very often contains arsenic.

The coloring of wall-paper with arsenical green or red is injurious, not only to those engaged in its manufacture; there are a sufficient number of cases known in which chronic poisoning

has been produced by living in rooms furnished with such paper, and still more easily by living in rooms, the walls of which are painted with arsenical water colors. I myself saw, two years ago, a case of this kind, where three persons, employed in the Court-House at Königsberg, suffered with undoubted symptoms of chronic poisoning. All of the chambers of the Court-House were painted yellow. Finally the following proved to be the explanation of the source of poisoning: The public documents heaped up in the repositories on the side of the walls had, by being placed in the compartments against the wall, gradually rubbed off the new yellow paint, and exposed to view an old green paint beneath; this was also continually being rubbed off, and there was found upon and in the papers and in the compartments of the repository a thick layer of green-colored dust, which, upon analysis by Dr. Blochmann (at that time assistant in the chemical laboratory at Königsberg), was found to contain 8.32 per cent. of arsenious oxide. This dust—partly contained between and in the folds of the papers—was diffused throughout the whole building by handling and carrying the documents, and would be found upon the table whenever a bundle of papers was opened upon it. Other entirely similar cases, in which the detection of arsenic in the urine has verified the diagnosis, have long been known. In all such cases it is probably the arsenical dust which causes the poisoning. Fleck has, however, proved that arseniuretted hydrogen in small amount is developed in a mixture of arsenious acid and starch paste, yet this proves nothing in regard to the conditions here under consideration. The dust also appears to play the principal part in all other forms of chronic poisoning, with the exception of those which are caused by taking the arsenic internally.

It is impossible to state the amount of arsenic necessary to produce chronic poisoning. Our knowledge of the conditions necessary for the understanding of the process is very incomplete. We frequently see the greatest variation in its effects upon different individuals. It is a well-established fact that in Styria and other places there are persons (the so-called arsenic-eaters), who from early youth take arsenic in amounts of even six grains daily, or very often at least, and yet arrive at an advanced age

and remain in good health. The doses which in other cases produce severe chronic poisoning are evidently much smaller; yet the above-mentioned amount of the poison is within the limit of a single fatal dose. It is everywhere stated that horses bear large doses of arsenic, and that it is often given to them to impart a well-nourished appearance.

In all cases arsenic-poisoning is only manifested under the immediate influence of the poison, and not—as in the case of lead, for example—years after the removal of the person from its influence. It is true, however, that complete recovery is never possible after the disease has reached a high degree.

No special predisposing conditions to the action of the poison are known, except the so-called individual idiosyncrasy, to which we must resort in this as in other forms of poisoning.

The *clinical history* of chronic poisoning also does not appear to be well established, at least in all of its details.

The usual results of the long-continued action of arsenic are angina, above all also conjunctivitis, and chronic gastric and intestinal catarrh, the latter characterized usually by constipation, but sometimes by diarrhœa. If the poison acts in the form of dust, it produces an eczematous inflammation of the skin, attacking preferably the most vulnerable parts, such as the folds of the scrotum and axilla, and leading to excoriation and a tendency to death of the superficial layers of the skin. In severe poisoning the deleterious action of the arsenic upon nutrition is never wanting: a grayish cachectic appearance, all kinds of anæmic troubles, headache, pain in the limbs, falling out of the hair and even of the nails, both with and without the formation of ulcers at the edge of the nails, mental depression and apathy, sleeplessness, etc., belong to the symptoms of such a case; weakness like that of paralysis, and imperfect sensibility, are frequently mentioned. True paralysis, limited to certain nerve-tracts, is a more frequent sequel of acute than of genuine chronic poisoning. In such cases it appears during the first few days, or sometimes not until later, during the second or third week, or even not until still later. Christison, who has given a good collection of the cases in question, mentions that of Dehaën, in which the first symptoms of commencing paralysis did not ap-

pear until after the patient had completely recovered from the symptoms of acute poisoning, and had felt entirely well for three successive days. Compare also the cases of Schaper.

The paralyses usually develop gradually, and without noticeable evidences of inflammation; these are, however, by no means always wanting, especially at the beginning and in paraplegic forms. Contractures are frequently mentioned, and remain permanent in cases which are not cured. Often a single extremity alone is affected. If the paralysis attacks several limbs, it is usually paraplegic; paralysis of all four extremities occurs. It is generally stated that the extensors are more severely affected than the flexors; atrophy of the affected limbs is frequently present, although it may be wanting even in complete paralysis which has lasted for years. Little is accurately known concerning the affection of the sensibility. The bladder and intestines are not affected.

In the majority of cases recovery from the paralysis takes place, yet a large number are known (Christison, Schaper, and others) in which it remained of constant intensity during lives which lasted many years.

Of the complications, pulmonary phthisis has been mentioned as the one most frequently occurring. General dropsy is always noticed as the final symptom, but nothing is known concerning its connection with renal disease.

Theoretical and Experimental Considerations.

Those facts which are known concerning the absorption and elimination of arsenic (arsenious acid) have already been mentioned; it need only be stated here, that the poison is, according to Bergeron and Lemattre, probably eliminated with the sweat, as well as with the urine and bile; we wish also once more to dwell upon the fact that arsenic does not, like the heavy metals, remain a long time in the living body, but is in the course of a few weeks completely eliminated.

It has been established experimentally, since the investigations of C. Schmidt, that an important part of the action of arsenic is to diminish the elimination of carbonic acid and urea

even during starvation, that is, to diminish tissue-metamorphosis. On the other hand, the not unequivocal fact was referred to, that the temperature of the body is lowered by taking small doses of arsenic. The most recent experiments of Boeck have, however, thrown some doubt upon this statement as to the action of arsenic in diminishing tissue-metamorphosis.

A further interesting property of arsenic is the fact, discovered by Saikowski, that in animals its use causes the speedy disappearance of glycogen from the liver. This depends upon the fact that the arsenic acid prevents the change of the sugar to glycogen. In some experiments performed by me with starving rabbits, which received on the third day of starvation or later an injection into the stomach every two hours of from one to two and a half drachms of sugar with three-tenths of a grain of arsenious oxide, there was always found in the liver a very small amount of glycogen, the maximum being 0.15 per cent. of the fresh tissue. No sugar appeared in the urine. Compare also Lehmann.

The observations made by Kunze are familiar—namely, that the heart of warm-blooded animals, killed immediately after the injection of small amounts of arsenic into the veins, continued to pulsate for a long time (twenty-four hours) after the death of the animal.

The power of arsenic acid to prevent fermentation, etc., is well known, so that it is natural that its above-mentioned action upon the living organism should be considered as connected with its property of arresting fermentation. But against this theory it should above all be remembered that the true processes of fermentation in the organism, such as the gastric digestion, are, according to Boehm and Schaefer, not arrested by arsenic.

In regard to the action of arsenic upon individual organs, Sklarek found that, when injected subcutaneously, it produced a slowing and cessation of the heart's action in frogs. It also produces paralysis of the nervous centres.

This effect of arsenic was first made known by the labors of Boehm and Unterberger. The failure of the heart depends upon the complete paralysis of the abdominal vessels, and its paralyzing effect remains limited to the vessels in this region, when it is injected into the blood as well as when it is taken into the stom-

ach; when applied by the latter method the poisoning takes place more quickly and more intensely. The elimination of the poison takes place from the blood through the mucous membrane of the stomach and intestine, but this is too slight to warrant the supposition that the local action of the arsenic so eliminated is of importance. On the contrary, Boehm favors the view that in all cases the symptoms of arsenic-poisoning here mentioned must be referred to the effect of the arsenic from the blood. Against this, however, it must be remarked that, when applied to the skin, it exhibits a local in addition to its general action.

Mention has already been made of the discovery of Saikowski, who found great fattening of the liver, kidneys, and muscular tissue; he found a larger amount of fat in the liver than in his experiments upon phosphorus-poisoning.

Free arsenic oxide does not possess any corrosive action; at least it forms no compound of albumen. Its powerful local inflammatory action upon the mucous membranes, as well as upon the skin, has not been sufficiently explained.

It follows from the above that it is at the present time impossible to give any theory which will satisfactorily explain arsenic-poisoning. The above-mentioned work of Boehm forms, however, a most important contribution in this respect. Yet in human poisoning it is impossible to consider the single symptoms separately as to whether they are to be ascribed to the local irritation or to the general action of the poison. There is no question that it does act as a local irritant; yet it is difficult to say in single cases how much of the inflammation of the stomach, after it is taken internally, for example, is dependent upon this and how much upon the general action. There is, moreover, no doubt that the symptoms of collapse depend directly upon its action on the heart and blood-vessels, or upon the nervous centres, but, on the other hand, it seems sometimes to depend also upon the violent gastro-enteritis, etc.

The *treatment* of chronic arsenic-poisoning can only be prophylactic. If anything shows the importance of sanitary laws, it is this fact that at the present time arsenical clothing, wall-paper, etc., are daily sold in the shops.

On account of the importance of this substance in many in-

dustries, and on account of its very low price at the present time, no attempt can be made to materially diminish the danger to workmen in the arsenic mines, except by the simplest means; in regard to what can be done in this respect, we must refer to the copies of the Saxon regulations.[1]

No antidotes are known; remedies to hasten its elimination are unnecessary. It may be mentioned that Mueller asserts that he has observed that potassium iodide hastens its elimination. In addition, therefore, to the prophylactic treatment—that is, sanitary regulations,—nothing remains, except that which is usually employed with persons who are feeble, and who suffer from those affections which go to make up the group of symptoms.

Arseniuretted hydrogen poisoning has thus far only been observed experimentally in animals, and as the result of handling it incautiously by the chemist in the laboratory. That arseniuretted hydrogen is the active agent in cases of poisoning by wall-paper is not proved, and is, moreover, to judge from the symptoms seen in such cases, highly improbable. Finally, the symptoms of simple chronic arsenic-poisoning are totally different from those of arseniuretted hydrogen poisoning. Of this we know only the acute form, which is caused by inhaling very small amounts of the gas, produced by the development of hydrogen in solutions containing arsenic, or in large quantities by treating the arsenide of zinc (an alloy of arsenic and zinc) with dilute sulphuric acid. The symptoms of arseniuretted hydrogen poisoning consist of vomiting with pain in the region of the stomach, headache combined with prostration, and abundant hæmoglobinuria. The last symptom must be due to the power of the arseniuretted hydrogen to decompose the blood-globule.

The cases which have been observed in human beings have usually proved fatal, but recovery frequently takes place in animals, if too much of the gas has not been absorbed, and if the hæmoglobinuria has not been too abundant.

The post-mortem examination leads to negative results. Nothing is known concerning treatment.

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[1] *Pappenheim*, I. p. 168.

VEGETABLE POISONS.

VON BOECK.

POISONING WITH ATROPINE.

Atropine, $C_{17}H_{23}NO_3$, is one of the most powerful vegetable poisons. It was discovered in 1831 by Mein, and in 1833 by Geiger and Hesse in the deadly nightshade (Atropa Belladonna). It forms colorless, columnar, and acicular crystals, glossy as silk; it has a bitter taste; is sparingly soluble in water, but readily so in chloroform, alcohol, and amylic alcohol. It is to be found in several plants, and for this reason, as well as on account of its frequent use in medicine, poisoning by it often occurs. Daturine, which was formerly regarded as an independent alkaloid, has been proved to be identical with atropine in its chemical as well as its physiological action.[1]

Etiology.

In Germany atropine is chiefly found in the Atropa Belladonna, which is very common in our woods, and the similarity of its berries to small black cherries leads to poisoning. A number of poisoning cases arising in this manner, especially among children, have been recorded; even the specimens cultivated in botanic gardens have sometimes occasioned poisoning. Orfila[2] describes in detail the effects of deadly nightshade berries upon 500 soldiers, who had plucked and eaten them in a wood near Pirna (Dresden). But poisoning has also often arisen from the leaves having been mistaken for the leaves of various innocuous plants.[3] The family of an Italian herb-collector, numbering five persons,

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[1] See the researches of *Planta*. Also *Husemann*, Pflanzenstoffe. p. 434.

[2] General Toxicology, translated by *Hermbstaedt*. Berlin. 1818. 3. Thl. p. 271.

[3] *Stokvis* in Amsterdam, Archiv für path. Anat. XLIX. 1869. S. 450; also Journ. de chimie med. 1869. Mai. p. 210.

were poisoned by food having been prepared in a vessel which had not been cleaned after having been used for boiling deadly nightshade leaves.[1] Cases of poisoning have also been recorded from human beings eating the flesh of animals which had fed on belladonna leaves without danger to themselves; among the animals to which atropine is innocuous are rabbits, pigeons, rats, and guinea-pigs. Some years ago this circumstance was the subject of a trial in an American court of law.[2] Bouchardat[3] mentions cases of persons having been poisoned by eating snails in vineyards, which had fed upon the leaves of the deadly nightshade.

There are numerous instances of poisoning by preparations of belladonna used medicinally, as, for instance, by taking too large doses of the extract, by mistaking a belladonna liniment for a draught to be taken internally, and even from its outward application. Indeed, cases are known in which poisoning has occurred from the application of a belladonna plaster to the skin, or the rubbing-in of belladonna liniments.[4]

Even the application of a solution of atropine to the eyes has frequently produced poisoning, either through simple absorption of poison by the conjunctiva, or by a portion of the atropine escaping through the small lachrymal ducts into the nostrils or the throat, and there becoming absorbed.[5]

Thus Richet[6] tells of an old man who had one drop of solution of atropine (1 : 100) dropped into his eye twice a day, and after eight days became violently delirious; the delirium disappeared with the discontinuance of the remedy. A similar case is recorded by Jos. Laurenzo of Bahia.[7]

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[1] *G. Martino*, Storia di sette persone avellenate dall' estratto di Belladonna e guarite. Ann. univers. di med. Juglio. 1872.

[2] Pharmaceutical Journ. and Transact. Ser. II. Part 7. p. 127.

[3] Compare *Husemann*, Handbuch der Toxikologie. Berlin, 1872. p. 281.

[4] *Peroud*, Americ. Journ. LXXXVIII. p. 403. Oct., 1862; *Lopez*, Americ. med. chirurg. Rev. March, 1860, p. 285; *Jenner*, Med. Times and Gaz. Nov., 1857; *Morisse*, Journal de Toxicolog. Avril, 1859; *Rossignol*, Lancet. 11 Nov., 1865; together with a number of other records.

[5] *Chassaignac Lauzer* in Revue thérap. 1854. p. 266.

[6] Gaz. des Hôpit. 79. p. 285. 1869.

[7] Gaz. des Hôp. 123. 1869.

Many cases of poisoning are also attributable to the thornapple (Datura Stramonium); they generally arise out of mistakes in cookery; especially the seeds of stramonium are very poisonous. Schneider, in Casper's Wochenschrift,[1] has contributed a tolerably full account of the pharmacological and toxicological records on this subject handed down to us from former times. Fresh instances have occurred in modern times; thus Ploegel[2] witnessed a case of poisoning by the tincture of stramonium; Leygey,[3] one by the seeds; Turner also,[4] Kuhorn,[5] Rogers,[6] and others.

Stramonium has also been employed for committing suicide, as in the case reported by Lichtenfels.[7] It has also been used as a poison with the intent of robbery or murder; for instance, the natives of India are in the habit of poisoning English soldiers with a sweetmeat containing the seeds of the thornapple for the purpose of robbing them; Th. Anderson gives a case of this kind.[8] On another occasion atropine[9] was given to an old man in his milk, and he died in five hours. Even by subcutaneous injection of atropine (daturine) very dangerous cases of poisoning have arisen.[10]

As to what constitutes a poisonous dose, it must be borne in mind that children can tolerate comparatively very large doses of belladonna, particularly when they are suffering from nervous complaints—chorea, for example; thus H. W. Fuller[11] observed that a girl ten years of age, suffering from chorea, took every day for twenty-six days 70 grains of the extract of belladonna = 1019 in all; another girl of fourteen took in eight days 37 grains without the smallest injury, whereas in the case of adults even 2 grains may produce unmistakable symptoms of poisoning.

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[1] Der Stechapfel als Arznei u. Gift. Casper's Wochenschr. No. 37. 1848.

[2] Wien. med. Halle. II. 42. 1862.

[3] L'Union. 6. 1862.

[4] Amer. Journ. of Med. Sciences. April, 1864.

[5] Bull. de Thérap. LXX. p. 285.

[6] Philad. Med. and Surg. Rep. Aug. 31. p. 211. 1872.

[7] Wiener Zeitschr. N. F. I. 37. 1858.

[8] Edinburgh Med. Journ. V. p. 1100. June, 1860.

[9] *T. Crace Calvert*, Pharm. Journ. 1872. pp. 596, 617, 663.

[10] E. g., *Charles Carrol Lee*, Amer. Journ. of Med. Science. Oct., 1862. p. 404.

[11] Med. Times and Gazette. July 23, 1859.

As a general rule, however, belladonna and atropine act as very powerful poisons, even in very small quantities. In a case given by J. Seaton,[1] one single nightshade berry was sufficient to produce severe symptoms of poisoning in a young man; in another case given by Bauer,[2] a child nine months old died in twenty-four hours from having eaten three berries. A teaspoonful of belladonna liniment swallowed by mistake killed a woman sixty years of age, in spite of all antidotes.[3] Yet it is a fact that sometimes very large doses can be borne, and that often cases which appear to be very serious end in recovery. Thus, a Berlin physician took nearly half a grain (0.03 gramme) of pure atropine and recovered,[4] whereas another[5] takes five and a half grains (0.36 gramme) of atropine and dies; a girl two and a half years old takes a fourth of a grain of atropine and recovers, in spite of very alarming symptoms.[6] A lady in Philadelphia takes instead of three grains of assafœtida, the same quantity of atropine, and dies in fifteen hours.[7] I myself witnessed a case in which a man, sixty years of age, who had taken by mistake one-quarter grain (= 0.015 gramme) of atropine, recovered, notwithstanding very violent symptoms. In general, we may say that one-twelfth of a grain of atropine may produce poisoning, but that death ensues very rarely even from three-quarters of a grain. Preparations of belladonna and stramonium naturally act according to the proportion of atropine which they contain. The root of the nightshade contains, according to Schroff, the most atropine (one part in three hundred), the leaves contain less; the various extracts and tinctures are again very different in strength; so that it is impossible to give any exact figures for them. Taylor saw a young man of sixteen, who had taken a drachm of extract of belladonna, die in three and three-quarter hours, while a woman

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[1] Med. Times and Gaz. Dec. 3. 1859.
[2] Würtemberg. Corresp.-Bl. 1873. p. 113.
[3] *Beddoe*, Lancet. 1870. July 16. p. 83.
[4] *Siegmund*, Virchow's Archiv. XLVIII. p. 188. 1869.
[5] *Pollack*, Wiener med. Presse. 1870. p. 565.
[6] *Kuethe*, Nederl. Tijdschr. f. Geneeskunde. Afd. 1. p. 497. 1870.
[7] *Gross*, Americ. Med. Journ. Oct. 1869. p. 401.

who had taken the same quantity recovered in twelve hours. The German Pharmacopœia fixes as maximum doses:

	Per dose.	Per diem.
Of belladonna leaves	0.2 (gr. 3).	0.6 (gr. 9).
Of belladonna extract	0.1 (gr. $1\frac{1}{2}$).	0.4 (gr. 6).
Of belladonna tincture	1.0 (♏ 15).	4.0 (♏ 60).
Of atropine sulphate	0.001 (gr. $\frac{1}{65}$).	0.003 (gr. $\frac{1}{22}$).
Of belladonna root	0.1 (gr. $1\frac{1}{2}$).	0.4 (gr. 6).

Atropine-poisoning takes place when the alkaloid has entered in sufficient quantity into the fluids of the body; the manner in which it enters the body is not of much importance; in addition to the ways already mentioned, poisoning may also be brought about by enemata of infusion of belladonna, and by suppositories which contain extract of belladonna.

The symptoms consequent upon the introduction of atropine usually set in somewhat rapidly, as absorption by the mucous membrane of the stomach and intestines proceeds with considerable rapidity.

Pathology.

Nature and Course of the Illness.

In general, poisoning by atropine produces effects similar to those of most other narcotic poisons. The poison first attacks the brain, especially the sensorium, but then it invariably influences the cardiac pulsations and the condition of the pupils.

As regards the sequence of symptoms, we way safely follow Schneller and Flechner,[2] who observed this sequence in experiments on themselves; and their statements, as to the more important data, have been confirmed by Bouchardat and Stuart Cooper[3] and Lusanna,[4] whose experiments are more recent.

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[1] *S. Taylor*, von *Seydeler*. III. Bd. p. 375.

[2] Beiträge zur Physiologie der Arzneiwirkungen. Zeitschrift der Wiener Aerzte. 1847. Juni.

[3] Recherches optiq., physiolog., thérap., et pharm. sur l'atropine. Gazett. med. de Paris. 1848. Nos. 51 und 52.

[4] L'Union méd. No. 77. 1851.

The first symptom is dryness of the palate, subjectively and objectively, furred tongue, tickling in the throat, hoarseness, difficulty in swallowing and speaking, nausea, inclination to vomit. These symptoms, especially the dryness of the throat and palate, generally set in fifteen minutes after the poisoning. They are usually attended with violent thirst.[1]

Brain symptoms next appear: giddiness, headache, slight stupor, confusion of mind, dejection; to these are added hallucinations of the sight and hearing, various in character, often of a cheerful nature. Then follow disturbances of the organ of sight: weak-sightedness, seeing things in a mist, and objective suffusion of the vessels of the conjunctiva and dilatation of the pupils; then follow in most cases difficulty in micturition, the urine often flowing drop by drop and with pain; and finally, peculiar appearances on the surface of the body are observed: dryness of the skin, scarlet redness, œdematous swellings, etc.

In severe cases the preceding symptoms are developed with considerable violence. Thus the dryness of the palate and throat amounts to absolute impossibility of swallowing (aphagia), not even liquids can be swallowed; many patients in this condition shrink so much from the act of swallowing, that they forcibly resist, if anything is offered to them; children, according to the observations of Schaeffer,[2] are inclined to bite. Objectively we find very little secretion on the reddened mucous membrane, in the region of the salivary glands, or on that of the mouth itself. The heart and the vascular system present a series of especially noteworthy symptoms; in the first place perhaps a slight retardation, but later on an enormous acceleration of the cardiac pulsations occurs, which in the human subject may rise to 150 and 190 beats per minute.[3] If the poisoning is fatal, the heart finally becomes paralyzed, and then the heart, before it absolutely ceases to beat, will perform its contractions more slowly but irregularly,

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[1] *Tissore*. Empoisonnement par la belladonne. Gaz. méd. de Paris. 1856. No. 12.

[2] *Sobernheim* also mentions such a case in his Handbuch der prakt. Arzneimittellehre. Berlin, 1847. p. 6, taken from the Gaz. méd. de Paris. 1835. No. 17.

[3] *C. Holthouse*, Med. Times and Gaz., Dec. 1859, observed in a child four years of age, who had been poisoned with from 3 to 4 grains (=0.18–0.24) of sulphate of atropine. a pulse of 170 per minute.

and with little energy. The vessels, especially the carotid and temporal arteries, throb very violently, the peripheral vessels are enlarged ; hence we get injection of the conjunctival mucous membrane, and great protrusion of the eyeballs. This enlargement of the vessels shows itself chiefly also on the surface ; the face is generally of a livid redness, and is subjectively and objectively hot ; but frequently the rest of the body also is covered with a scarlet exanthem, which either affects the upper part of the body only or, in rare cases, extends to the lower part. In spite of this hyperæmia of the skin, perspiration is suppressed, and the skin is dry to the touch. These cutaneous symptoms often follow upon very small doses of atropine. Thus Sidney Ringer [1] asserts that $\frac{1}{200}$ grain (=0.0003) of atropine subcutaneously injected arrests perspiration, and J. G. Wilson [2] saw two cases of lying-in women, who had had belladonna ointment rubbed on their breasts to produce galactostasia, and upon whom a scarlet eruption came out, which lasted three or four days, and disappeared sooner than the dilatation of the pupils. Th. Stadler [3] saw a similar eruption appear upon a child three months old, within a few minutes after the administration of $\frac{1}{200}$ grain (= 0.0003) of atropine sulphate for whooping-cough. It lasted five hours ; smaller doses brought out a similar eruption each time, but of shorter duration. A desquamation of the epidermis often succeeds this eruption.

Corresponding to the condition of the heart and the vessels, the pulse—which at first was full and hard—becomes soft, easily compressible, the blood-pressure is considerably reduced, and the temperature of the body is invariably diminished.

The distention of the jugular vein, which has been observed in many cases,[4] and the swelling of superficial veins generally [5] with occasional œdema,[6] are referable to the depression of the action of the heart and diminished pressure of the blood.

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[1] On the Influence of Belladonna in Sweating. Practitioner. July. p. 93 1873.

[2] Two cases, etc. Glasgow Med. Journ. Feb. p. 198. 1872.

[3] Med. Times and Gazette. April 11, 1868

[4] *Bonassies*, Empoisonnement par la belladonne. Journ. de Chim. Med. Nov. 1844.

[5] *Trapenart*, L'Union. 1859. p. 147.

[6] *Storer*, Brit. Med. Journ. May 4, 1870.

With regard to respiration, its frequency is, in the early stage of the poisoning, diminished; subsequently it is steadily increased till towards the final stage, when it again sinks to the normal rate, or becomes slower and slower till it ceases altogether.

We also find in many cases a severe laryngitis excited, together with pain in the larynx, roughness and hoarseness of the voice, and the separation of a white transparent secretion from the mucous membrane of the larynx and bronchi; this was observed in two cases by Morel.[1]

One of the most distinctive symptoms of atropine-poisoning is dilatation of the pupils, which, even with minimum doses (according to Donders $\frac{1}{130000}$ gr. =0.00000046), lasts for several hours. When it is dropped into the eye, only the one pupil is dilated, whereas in cases of general poisoning by atropine, both eyes are almost always equally affected. If somewhat larger quantities are introduced, the pupils are dilated to the maximum, remain motionless, no longer react to light, and thus a number of other symptoms are developed; for instance, a variety of disturbances in the power of seeing, utter incapability of focalizing the eye, prismatic vision,[2] double vision, occasionally micropsia, and sometimes complete amaurosis. This mydriasis with its consequences sets in quite constantly, and may last a very long time: thus, for example, Gubler[3] states that in one case it lasted fourteen days; at any rate, it is the symptom of atropine-poisoning which is the last to disappear; indeed, it has been observed to last as long as three or four weeks. The supposed amaurosis of many observers[4] is only apparent, and is the result of the loss of the power of focalizing.

The chief effect of atropine, that upon the brain, manifests itself in a double form: first, a series of disturbances appear in the sphere of motility, and then considerable disturbances arise

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[1] Trois cas d'empoisonnement par la belladonne. Annal. de Société med. de Gand. 1872, Sept. 181.

[2] *Stokvis* mentions, Arch. f. path. Anat. XLIX. p. 450. 1869, a case of a man who saw the edges of all objects prismatically colored.

[3] Commentaires thérapeutiques du codex medicamentarius. Paris. 1874. p. 746.

[4] *Evans*, Brit. Med. Journ. Sept. 21, 1861.

in that of sensibility. With regard to the motile changes, the most striking point is that, as a rule, soon after the setting in of the first symptoms of poisoning, a general jactitation of the body takes place, in many cases accompanied with pains: crying and screaming, especially with children, are common. Many patients in this jactitatory state make free use of their muscular strength, crush to pieces all that comes into their hands; but shortly after there supervenes a disturbance in the co-ordination[1] of these movements; many lose the power of walking straight, stagger about, cease to be able to articulate clearly; even cases of aphasia[2] and alalia are recorded. More rarely, convulsions occur, generally clonic,[3] seldom tonic spasms; still tetanus, especially opisthotonos, has been seen. Sometimes very peculiar disturbances of the locomotor system appear; thus a miser, who intended to steal turnips in a field, but pulled up hyoscyamus roots instead, paid the penalty of the theft by being seized with a dancing-frenzy accompanied by convulsive laughter.

Dysphagia also is sometimes the result of contraction of the muscles of deglutition, for in the Tissore case, when a finger was passed into the gullet, it was found to be firmly contracted, so that an emetic could only be administered by an œsophageal tube. So also the dysuria, which occurs in so many cases, is to be attributed to cramp of the detrusor vesicæ urinariæ.

The symptoms connected with the psychical functions of the brain are more constant and more important. The first symptom is generally giddiness, swimmings in the head, abnormal sensations, especially of sight and hearing; hallucinations are also very common, and delirium is superadded, so that the general

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[1] See, for example, the case of Stevens (referred to on p. 680).

[2] *Paget-Blacke*, Reports of St. George's Hospital. III. 160. 1868. An asthmatic patient took about one drachm and a half of tincture of stramonium. The usual symptoms followed; later on actual aphasia set in, so that he called everything by the wrong name.

[3] In a case described by *Trapenart* (l'Union. 147. 1859), of a lunatic, thirty years of age, who had eaten some nightshade berries, trembling of the hands and twitchings in the whole upper part of the body came on; the same thing occurred in the case of a girl who had taken ½ gr. of atropine (*Kuethe*, Nederland. Tijdschr. f. Geneesk. Afd. I. p. 497. 1870). In the case, already cited, of *Bonassies*, cramps in the fingers came on, which gradually extended to the trunk and the other parts of the body.

condition may be characterized as one of mental aberration with delirium.

These attacks of delirium may be quiet or they may be violent, and they sometimes continue till coma sets in.

After the jactitation has lasted for some time—the length of time depends upon the quantity of the poison—it gives place to lassitude and a feeling of sleepiness, which generally passes into complete sleep; the stage of narcosis. This sleep becomes gradually deeper, patients cannot be roused from it by any means, the eyelids are only half closed, and this somnolent and comatose condition, in which, with the exception of the so-called automatic action of the heart and of the respiratory muscles, there is no voluntary or reflex movement, again disappears gradually, or ends in death. In many cases, especially those that end fatally, the contents of the bladder and of the bowels are passed involuntarily, in consequence of paralysis of the sphincters in this stage of narcosis. In a few cases fits of delirium and stupor alternate, and these intermitting or remitting cases are those in which the prognosis is more favorable. Among the rarer symptoms of atropine-poisoning we may mention erotic manifestations which take place during the stage of excitement, priapism,[1] etc. Parsons[2] gives an instance in which a man's hair turned gray during atropine-poisoning of short duration. A case communicated by Evans[3] is also worth mentioning, in which a girl nine years of age had eaten four nightshade berries, and after six hours tympanites in an aggravated form set in.

As regards the duration of the poisoning process, death generally ensues within twenty-four hours, rarely within five or six hours, and more rarely still not for thirty hours. Convalescence is always very slow, never sudden; the pulse and respirations very gradually return to their normal rate; subsequently sensibility is restored, and the sensorial disturbances cease. There are cases in which, after somewhat large quantities of atropine have been taken, four days, and even more, are required for recovery.

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[1] *Schmid.* Monatsblätter für Augenheilkunde. II. p. 158. May, 1864.

[2] Brit. Med. Jour. 25. Dec., 1869. p. 675.

[3] Ibid., 21. Sept., 1861.

As sequelæ, mydriasis lasts for some time, sometimes accompanied by slight focal disturbances. The aphasia which we mentioned above lasted for a considerable time, and the patient, during his convalescence, called almost everything by the wrong name. There are, therefore, no actual sequelæ in cases of atropine-poisoning, although occasionally hemorrhage in the brain has occurred, followed by prolonged hemiplegia, yet these are only indirect results of the poisoning.

Atropine kills by paralyzing the heart in the first place, but perhaps also, in some cases, by exhaustion of the respiratory centre.

Analysis of Symptoms.

Character of Atropine-Poisoning.

Recent experimental investigations supply a fairly satisfactory pathological basis for a number of the symptoms of atropine-poisoning. Another large group of symptoms, however, must simply be accepted as fact.

The dryness of the palate is to some extent accounted for by the experiments which Heidenhain, Bezold and Bloebaum, Keuchel also, have made on the salivary glands of animals. We know by the researches of Ludwig, Czermak, Bernard, that irritation of the tympanico-lingual nerve which arises from the chorda tympani, and accompanies the trigeminus, leads to the secretion of a quantity of thin saliva in the submaxillary gland, at the same time accelerating the flow of blood through the gland and heightening its color.

Heidenhain[1] has shown that irritation of the fibres of the chorda tympani in atropine-poisoning accelerates the flow of blood, but does not cause secretion of saliva, whereas excitement of the sympathetic causes the secretion of a small quantity of thick viscid saliva as in the normal condition. Keuchel had before observed this fact.[2]

The mydriatic effect of atropine is a favorite subject for experiment.

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[1] Arch. f. d. ges. Physiolog. V. 40.

[2] Das Atropin und die Hemmungsnerven. Dorpat. 1868.

Hitherto the view has been universally accepted that dilatation of the pupil follows directly upon the use of atropine, but Rossbach and Froehlich maintain that in the case of frogs and rabbits dilatation is preceded by contraction, slight and transient indeed, but quite perceptible when very small doses of atropine (one-one-hundredth and less) are administered.

Whether this proceeds from paralysis of the oculo-motor nerve, or from excitement of the sympathetic, or from both factors simultaneously, is still a subject of controversy. It is pretty clearly proved that the sphincter iridis and its nerve, the oculomotorius, are paralyzed by the poison. Indeed, the circumstance that the tensor chorioideæ, supplied by the same nerve, becomes also paralyzed, strongly supports this view ; but still more the fact (according to de Ruiter's experiments), that an electric shock given to the iris while the eye was under the influence of atropine produced no contraction of the pupil, which always occurs when the eye is in the natural condition. Lastly, the absence of all reaction to the impression of light, even when the sympathetic has been divided, affords almost certain proof to the same effect. The most direct proof of this theory, however, is furnished by the experiments of Bernstein and Dogiel ;[1] these investigators irritated the oculomotorius within the cranium of the atropinized animal, without producing contraction of the pupil. That the muscle of the iris, as such, is not paralyzed, the authors just mentioned prove by the fact that in the same experiment direct excitation produced contraction of the pupil.

The second question, whether atropine does not simultaneously excite the sympathetic and the dilatator pupillæ supplied by it, is more difficult to answer. In favor of this view, the testimony of Cramer[2] may be quoted, who says that after section of the cervical sympathetic on one side, followed by atropine-poisoning on the side operated upon, a slighter mydriasis followed than upon the uninjured side. Another argument for this theory is, that the extent of dilatation of the pupil cannot

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[1] *Bernstein* und *Dogiel*, Verhandlungen des nat. med. Vereins zu Heidelberg. IV.

[2] Het accomodatic Vermogen der oogen. Haarlem. 1853. 127.

well be accounted for by a mere preponderance of the action of the dilatator consequent upon the inaction of the sphincter, and also that no further dilatation can be produced by direct excitation of the iris, because the dilatator has already been contracted to its maximum. But doubt is again thrown on this conclusion when we remember that Gruenhagen[1] and Hirschmann[2] both succeeded in increasing the dilatation caused by atropine by exciting the sympathetic, and that H. Braun,[3] moreover, proved that, six months after the section of the sympathetic, by which time the terminations of the sympathetic in the pupil must have been long degenerated, dilatation still followed the use of atropine. For the present, therefore, we must regard the influence of atropine on the dilatator pupillæ as doubtful, even though Braun's experiment may seem to point to the opposite conclusion.[4]

The fact that, in local application of atropine to one eye, dilatation of the pupil of only that eye followed, combined with the observation made by Fleming,[5] that when he very carefully conveyed the poison only to one side of the eye, dilatation of the pupil first appeared on that side, seems to indicate a local action of this poison. But then, again, we are almost compelled to admit, with Bezold and Bloebaum, supported by L. Hermann,[6] that nervous centres exist in the iris itself; that these really must reside either in the iris or its immediate neighborhood, is proved by Ruiter's statement,[7] that even in an excised frog's eye mydriasis can still be produced, when all other nerves are ex-

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[1] Centralbl. f. d. med. Wissenschaft. 1863. 577.

[2] Arch. f. Anatomie u. Physiol. 1863. 309.

[3] Arch. für Ophthalmolog. V. 112.

[4] Strong evidence of active contraction of the dilatator by atropine is afforded by the often observed fact that the passive dilatation ensuing upon paralysis of the oculo-motorius is never as great as that induced by atropine, and that in such condition the dilatation is greatly increased by atropine, whether locally applied or introduced into the general circulation. The writer of this note has, with many others, proved such increased dilatation by local applications of atropine to human eyes affected by idiopathic absolute paralysis of the oculo-motorius.—E. Curtis.

[5] Edinburgh Med. Journ. 1863.

[6] Lehrb. d. experiment. Toxikologie. Berlin. 1874. p. 335.

[7] Nederlandsch. Lancet. III. 433; also loc. cit. p. 83.

cluded. It is very probable, therefore, that atropine exerts its chief influence upon these nerve-centres. The loss of power of accommodation, disturbances of vision, etc., which have been observed in atropine-poisoning, are the result of the dilatation of the iris and paralysis of the tensor chorioideæ.

The action of atropine upon the heart and its movements has been reduced to a sound pathological basis by experiments on animals. Von Bezold and Bloebaum, and Keuchel, are the chief authorities for the action of atropine upon the heart.

The acceleration of the pulse following upon section of the vagus in otherwise healthy animals was not increased by atropine-poisoning afterwards;[1] again irritation of the vagus in atropinized animals failed to retard the pulsation of the heart. This proves that the extremities of the vagus in the heart after a slight excitation, which produces the transient and not very important retardation of the pulse at first, must have been paralyzed by the poison. Rossbach and Froehlich were the first to call attention to the original initial irritation of the extremities of the vagus. The question, whether the extremities of the branches of the vagus or the intermediate ganglia are paralyzed by atropine, is decided by Boehm's[2] experiment in favor of the former. He failed to arrest the atropinized heart of a frog by irritating the sinus. Schmiedeberg[3] was equally unsuccessful with muscarine.

While atropine is found to be incapable of acting on the sympathetic, its influence on the excito-motor ganglia of the heart is considerable. Von Bezold and Bloebaum (loc. cit.) have shown that these centres of cardiac innervation are completely paralyzed by tolerably large doses of the poison: the pulsations of the heart and the pressure of the blood diminish, when atropine is administered to an animal after section of the vagus and the cervical marrow.

But the cardiac muscle also loses its excitability and becomes

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[1] Exactly the opposite has been affirmed as the result of experiments by Lemattre (*Archives Générales*, August, 1865) and H. C. Wood (*Therapeutics, Materia Medica and Toxicology*, Philadelphia, 1876, p. 234).—E. C.

[2] Studien über die Herzgifte. Würzb. 1871. p. 14.

[3] Berichte der sächs. Acad. d. Wissenschaft. Math. phys. Classe. 1870. 129.

paralyzed under large doses. It appears, then, that atropine is eminently a heart-poison, which destroys life by arresting the action of the heart.

Von Bezold and Bloebaum have further proved by direct observation that atropine-poisoning in large doses is followed by distention of the small vessels, and that this distention is the consequence of paralysis of the vaso-motor nerve-centre, as the distention after injection of atropine into the peripheral end of the carotid takes place almost instantaneously. Accordingly, the pressure of the blood also decreases. Yet the blood-pressure does not decrease immediately after atropine poisoning; on the contrary, it increases in the first instance, or, when small doses are used, corresponding to the frequency of the cardiac pulsations, and to the initial contraction of the arteries.

The contraction of the arteries has been demonstrated by Meuriot,[1] at least in the case of the web of the frog, upon application of atropine. Fleming[2] and Hayden[3] had already observed this contraction; the latter holds the contraction of the vessels to be a reflex action of the skin.

This retardation of cardiac and vascular action fully accounts for the lowering of temperature observed in human subjects.

The influence of atropine upon the respiratory organs, which in human subjects as in animals shows itself first by retardation, afterwards by acceleration, depends upon a paralyzing action on the pulmonary branches of the vagus, so that the peripheral stimulation fails to reach the central organ; hence the retardation in the first instance.

The subsequent acceleration, demonstrated by the researches of Bezold and Bloebaum, is caused by the irritant action of the poison on the respiratory centre. When the dose is very large, however, this central organ is paralyzed, whether by the poison itself or by exhaustion, or by carbonic acid poisoning, attendant on the onset of cardiac paralysis.

The laryngeal fibres of the vagus, which in the normal condition have a retarding influence on respiration, are not paralyzed

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[1] Gaz. hebdomad. 1868. Nos. 12, 15, 16.

[2] Edinburgh Med. Journ. 1863. 777.

[3] Dublin Quart. Journ. 1863. Aug.

by atropine, as Keuchel[1] has proved; therefore they have nothing to do with the acceleration of breathing. Thus, also, the variations in breathing, observable in atropine-poisoning, are easily and naturally explained.

The influence of atropine upon the striped muscles and the motor nerves, which, as we have seen, in atropine-poisoning in human subjects takes the form of cramp, but which usually passes, after a short period of jactitation, into an absolutely motionless condition, is not very satisfactorily explained by the experimental evidence which we so far possess. Von Bezold and Bloebaum's experiments indicate, indeed, a diminution of the excitability of the motor nerves, but show that the muscle itself is scarcely acted upon by atropine; as regards the motor nerves, these authors show that it is highly probable that the terminations of the nerves in the muscle primarily suffer diminution of their excitability, and that subsequent changes occur in the nerve-trunk. This loss of excitability in the motor nerves helps to explain the motionless state of those poisoned, but it does not explain the occurrence of the convulsions; these are to be traced to changes in the nerve-centres.

The inquiry into the action of a poison upon the sensory nerves is extremely difficult, and as the methods hitherto adopted are not altogether unexceptionable, the statements of Botkin[2] and v. Bezold and Bloebaum (loc. cit.) on this subject are insufficient, though it appears fairly deducible from them that the excitability of the terminations of the sensory nerves is diminished by large doses of atropine. Still, practical clinical experience, especially in neuralgia, is calculated to give a stronger support to this theory than experiments on animals.

Lastly, the influence of atropine on the brain and the spinal marrow is very considerable, yet it presents even more obstacles to experimental research than that on the sensory nerves. In the human subject there are unmistakable symptoms of increase of excitability, and especially of actual excitement of the central portions of the nerves of the organs of sense, which is succeeded

[1] Das Atropin und die Hemmungsfasern. Dorpat. Diss. 1866.

[2] *Botkin*, Ueber die physiolog. Wirkung des schwefelsauren Atropins. Virch. Archiv. Bd. XLII. 1862.

by diminished excitability, sometimes passing into complete loss of consciousness and feeling. This effect upon the brain cannot be traced to disturbance of the circulation, but to direct action of the poison on the nervous elements. The spinal marrow also seems to be subjected to a like influence; according to Fraser[1] the convulsions which have been observed in human subjects also appear in the frog after large doses, but not till towards the close of the action of the poison; they begin with rigidity of the forefeet, then of the hindfeet, and tetanus is easily brought on by touch, while spontaneous movements are very labored or quite impossible. This convulsive stage, which may last for hours and days, is decidedly to be regarded as of a reflex character, dependent on increased excitability of the spinal marrow. Thus delirium, hallucinations, etc., are accounted for.

A few words must be said as to the influence of atropine on the organs composed of unstriped muscle. v. Bezold and Bloebaum found in atropinized animals the intestine in complete repose, and even after section of the splanchnic no movements set in. From this they conclude that the motor nerves of the intestine are paralyzed; in the next place the poison paralyzes the intramuscular ganglionic cells, and later the muscular fibres themselves, this paralysis being transmitted to these muscles just as the paralysis of a motor ganglionic cell of the spinal marrow extends to the corresponding muscles. When Keuchel administered small quantities of atropine, the peristaltic action of the intestine did not cease, but the existing movements could not be arrested by irritating the splanchnic; hence he concludes that it exerts a paralyzing influence on the nerve which checks the movement of the intestine and its peripheral extremities. The discovery of the paralysis of the detrusor vesicæ urinariæ, after previous violent irritation, is the result of clinical observation, not of experiment.

Results of Autopsies.

Frequent as poisonings by atropine are, very few post-mortem examinations are on record.

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[1] Trans. of the Royal Society of Edinburgh. XXV. p. 449; and Journ of Anat. and Physiol. 1869. May. 357.

Most of the reports of autopsies which we possess refer to persons who have died of eating belladonna berries or stramonium seeds. In these cases the stomach and intestinal mucous membrane are usually stained with the color of the berries, or else seeds of the thornapple or of the deadly nightshade are found in the intestinal canal. This is pretty nearly the most important result of these examinations.

Most of the other results that have been published are by no means characteristic: thinness and fluidity of the blood, which Seaton[1] mentions, injection of the skin of the face, engorgement of the blood-vessels of the brain and its membranes, an excessive quantity of fluid in the ventricles, some fluid in the pericardium, more or less hyperæmia of the lungs, liver, kidneys, etc. These results are too general to furnish satisfactory evidence in a court of justice. Kuerner[2] reports that he performed a post-mortem examination on a boy three years of age, and found that the vagus nerve had a strikingly red appearance in comparison with the phrenic nerve. It is self-evident that such a discovery is of no importance, as it may be merely accidental. Then he found thin fluid blood in the auricles, while the ventricles of the heart were empty. Otto[3] observed marked hyperæmia of the cerebral sinus, of the pia mater, of the medulla oblongata, as well as ecchymoses on the pericardium. Bauer[4] lays stress upon the strikingly rapid occurrence of putrefaction. The greatly dilated pupils observed in life generally continue after death. It is clear, then, that we cannot establish the existence of poisoning by atropine simply from post-mortem examinations.

Diagnosis and Differential Diagnosis.

Atropine-poisoning is recognized by a state of intoxication, accompanied with delirium and dilatation of both pupils.

Atropine-poisoning might possibly be confounded with ordinary alcoholic poisoning; but the history of the case, the absence

[1] Med. Times and Gaz. Dec. 3, 1869.

[2] Vergiftungen durch Beeren der Tollkirsche. Würtemberg. Corr.-Bl. 1856. No. 35.

[3] Vierteljahrschrift für gerichtliche Medicin. N. F. V. 1. p. 154. 1866.

[4] Würtemberg. Med. Corr.-Blatt. 1873. p. 113. No. 75.

of alcoholic odor, and the dilatation of the pupils, are sufficient indications to the contrary. Again, it might be mistaken for those affections of the brain which are associated with increase of intracranial pressure, therefore with simple congestion or with apoplexy. The absence of any affection of the arteries, the state of the pupils, the dryness and redness of the mucous membrane of the mouth, the quick breathing, may serve to elucidate the case.

Atropine-poisoning has very often been mistaken for cerebral disease,[1] therefore the chief stress is to be laid on the condition of the pupils.

Taking the temperature of the patient will be a sufficient safeguard against mistaking it for scarlet fever. It is more difficult to distinguish atropine intoxication from that produced by other narcotics; the diagnosis also becomes difficult if atropine has been applied to the eyes before the poisoning. Sidney Ringer[2] mentions a case in which it was for a long time impossible to diagnose atropine-poisoning in a woman, who had previously been operated upon for cataract.

The surest test of atropine-poisoning is when the unaltered urine acts mydriatically upon the cat's eye. That takes place when the urine contains one part of atropine in 130,000 parts (de Ruiter and Donders).

Of course, in diagnosing atropine-poisoning, we must ascertain whether atropine has been previously used medicinally.

A frequent and most practical method of establishing our diagnosis is to inspect the matters vomited or discharged by the bowels, amongst which we may often discern the skins of the berries, or the seeds that have been eaten.

Prognosis.

The prognosis of atropine-poisoning must be determined chiefly by the quantity of the alkaloid taken, but still more by the quantity of the poison actually absorbed.

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[1] *Gosset Brown*, Lond. Hosp. Rev. II. p. 169.—*Morgan*, Brit. Med. Journ. Dec. 1, 1866.

[2] The Accidental Poisoning of Dr. Sharpey. Lancet. Sept. 27. p. 469. 1873.

If vomiting comes on in the early stage, it is in favor of the patient; diarrhœa may also act favorably.

During the course of the case, we must rely chiefly on the condition of the respiration and circulation.

In general, the prognosis is not very unfavorable, since recovery has occurred even after very large doses, and since, notwithstanding the most dangerous symptoms, a happy result is by no means uncommon.

Treatment.

If the poison has been introduced by way of the stomach, the stomach-pump and emetics must be used, in order, if possible, to remove the poison before its absorption. Aperients are also advisable to remove any berries, seeds, etc., that may possibly remain in the intestinal canal. In the second place, the poison itself must be, if possible, neutralized.

According to Sinogowitz,[1] iodine is the best antidote, because iodine gives in solutions of atropine a thick, reddish precipitate; but Morel[2] recommends tannin, and reports three cases which were cured by it. Tannin throws down a white flaky precipitate in atropine solutions, on the addition of a little acid.

Garrod[3] speaks of two persons who had been poisoned by taking, the one, nine grains, and the other two and a half drachms of belladonna leaves, and whom he cured with animal charcoal; this is supposed to counteract the effect of infusion of belladonna. Thompson[4] recommends solution of caustic potash, to be given every two hours in milk, and says that this will destroy the alkaloid, and speedily remove the symptoms of poisoning. It is certain that alkalies decompose atropine outside the body.

Tannin and animal charcoal are decidedly the best remedies, as they are innocuous in themselves, and the first at least is readily procurable everywhere.

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[1] Med. Zeit. des Vereins in Preussen. 1854. p. 70.

[2] Trois cas d'empoisonnement par la Belladonne. Annal. d. Société de méd. de Gand. Sep. 1872. p. 181.

[3] Bull. de Thérapie. LIV. Fev. 1858. p. 168.

[4] Lancet. 1859. Dec.

If the poison has entered into the fluids of the body, the functional antidotes have to be considered. C. M. Stevens [1] reports the case of a woman, twenty-eight years of age, successfully treated by opium and veratrine. When these two drugs are given together it is impossible to determine the influence of the veratrine. We can scarcely believe, *a priori*, that veratrine exerts a special influence upon the action of atropine, even though we must acknowledge that the effect of veratrine is to lower the action of the heart. We ought apparently to attach more value to preparations of the calabar bean as antidotes. Frazer,[2] for example, reports that dogs, to which he gave a large quantity of calabar, bore it very well when it was administered in combination with atropine; one dog survived the administration of 8 grs. (=0.5) of atropine and 6 grs. (=0.36) of extract of physostigma. Similar results are reported by Bartholow.[3] Lorentenz [4] gives the case of two women who had taken a considerable quantity of atropine (in one case three-quarters of a grain), and who recovered very rapidly after he had given them two doses of 25 drops each of calabar tincture, and 3 and 5 drops respectively of a solution of calabar extract in glycerine (1 : 2).

In fact, the calabar bean, by virtue of the alkaloid physostigmine or eserine, which is its active principle, gives rise to a series of phenomena which appear to counteract the effect of atropine. Calabar promotes the flow of saliva, causes contraction of the pupils through spasm of the oculomotorius, sets up spasm and contraction of the vessels, and retards the cardiac pulsation and the respiratory action (see Calabar-Poisoning). v. Bezold and Goetz,[5] and subsequently Arnstein and Saststschinsky,[6] found that the active principle of the calabar bean retarded the pulse by irritation of the vagus; they found also that in mammalia

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[1] Boston Med. and Surg. Journ. Aug. 10, 1871. p. 81.

[2] The Practitioner. IV. 67. 1870.

[3] Ibidem. V. 25. 1870.

[4] Hospit. Tijdschr. XIII. 129. und Nord. med. Ark. III. 5. p. 58. 1870.

[5] Ueber einige physiologische Wirkungen des Calabargiftes. Centralbl. f. d. med. Wiss. 1867. No. 16.

[6] Ueber die Wirkung des Calabar auf die hemmenden und beschleunigenden Herznerven. Centralblatt f. d. med. Wiss. 1867. No. 40.

calabar counteracted the effect of atropine. On the other hand, Boehm[1] considers physostigmine, as well as atropine, to be one of the poisons which paralyze the extremities of the vagus; others—B. Tachau[2] and Roeber,[3] for example—attribute the retardation of the cardiac pulsation to paralysis of the motor cardiac ganglia, etc. Thus, at present, the most contradictory views as to the action of this poison exist, so that, from theoretical grounds, the value of physostigmine in cases of atropine-poisoning seems to be, as yet, doubtful. This view is strengthened by the researches of Rossbach and Froelich,[4] who maintain that physostigmine does not counteract the influence of atropine upon the heart (but has, to some extent, just the contrary effect), and they did not succeed in producing contraction of the pupils by applying physostigmine to an atropinized eye. Thus no positive results have been arrived at in the human subject, and it remains to be seen whether future investigation will furnish clearer evidence. We must not omit to notice Preyer's[5] recommendation of prussic acid as an antidote to atropine. The chief effect of prussic acid, as is well known, is to paralyze the respiratory centre and to stimulate the vagus; therefore it would appear, *a priori*, to be likely to exert an influence on atropine-poisoning. But this antagonism is denied by Keen and Hare[6]), as it had been before by Lecorché and Meuriot.[7] Preyer's theory has also been disputed from the experimental point of view by Bartholow[8], Schroff, jun.,[9] Knie, and Boehm.[10] But, on the other hand, Preyer[11]

[1] Studien über Herzgifte. 1871. p. 80 ff.

[2] Versuche üb. d. Wirkung d. Calabarbohnenextractes. Heilk. 1865. pp. 69–78.

[3] Ueber die Wirkungen des Calabarextractes auf Herz und Rückenmark. Diss. Berlin. 1868.

[4] Pharmacolog. Untersuchungen. 1 Heft. Würzburg. 1873. p. 77.

[5] Die Blausäure physiologisch untersucht. 1868 u. 70.

[6] Amer. Jour. of Med. Science. Oct. 1870. p. 442.

[7] Étude physiolog. et thérap. sur l'acid cyanhydrique. Archiv. génér. de méd. Paris. 1868. Vol. 1. pp. 529 551.

[8] Note on Atropia and its Physiological Antagonists. The Practitioner. London. July, 1870.

[9] Medic. Jahrbücher. Jahrg. 1872. pp. 420–513.

[10] *Knie*, Respirationsgifte I. Atropin, Blausäure. Dissert. Nov. 1873. Dorpat; and *Boehm*, Archiv für experimentelle Pathologie u. Pharmakologie. II. Bd. pp. 129–148. 1874.

[11] Ueber den Antagonismus der Blausäure und des Atropins. Ebenda. III. Bd. pp. 381–396. 1875.

has quite recently repeated his assertion, and supported it by experiments. He has shown that guinea-pigs and rabbits, after subcutaneous injection of watery solution of atropine (two and two-thirds fluidrachms of a five-grain atropine solution), may have deadly prussic acid administered to them without succumbing, and that with still larger doses of prussic acid, the action of the poison is protracted if atropine is given. We have not as yet made any practical use of this antagonism of prussic acid in the medical treatment of atropine-poisoning, nor shall we be likely to do so since prussic acid is itself so poisonous an agent. On the other hand, atropine may more safely be recommended as an antidote to prussic acid, and Preyer's researches tend mainly to this end.

The treatment of atropine-poisoning by morphine and opiates is of much greater practical importance. Attention has recently been called to this antagonism, and chiefly by the reports of Thomas Anderson,[1] who cured a case of opium-poisoning, in a man suffering from delirium tremens, by belladonna. His breathing gradually became more normal, etc. Since then both poisons have been reciprocally examined, both therapeutically and physiologically, but the results of the two methods have not harmonized. While, on the one hand, almost all the practitioners who have had the opportunity of testing the antagonistic properties of both poisons, agree, with hardly a dissentient voice, as to their real antagonism, the theorists, on the other hand, basing their opinions upon experiments on animals and upon ratiocination, have come to a totally different conclusion. The chief ground of this difference lies partly in the varying degrees of susceptibility in the animals subjected to experiment—for rabbits, dogs, cats, and pigeons are not equally, sometimes not at all, affected by the same poisons—and in part it lies in the different conception of what is meant by antagonism. Whereas practitioners in general regard the preservation of life after fatal doses as the true criterion of an antidote, most pharmacologists claim from an antidote that it shall affect the same organs in a directly opposite sense to that of its antagonist. They require, for example, that

[1] On the Influence of Belladonna Counteracting the Poisonous Effects of Opium. Monthly Journ. April, 1854. p. 377.

morphine shall paralyze the very same nervous apparatus which atropine excites, and *vice versa*, so that, with accurate dosing, the effect of both poisons must be nil. To others it does not matter how the antidote works, provided only that the general effect upon the organ is contrary to that of the first poison. With regard to morphine and atropine[1] a real antagonism probably only exists between them in respect to their influence on respiration; with regard to the pupil, the antagonism is only functional, because the two poisons appear to affect quite different nerve-elements.

That morphine, cautiously used, does good in atropine-poisoning, cannot, I think, be denied in the face of existing evidence, however sceptically disposed we may be on the subject. Thus Frommhold[2] has collected eighteen cases of belladonna-poisoning, which took a favorable course under the opium treatment. And since that time numerous cases in confirmation of this view have been recorded in medical journals. Almost all authorities agree that the most important condition of rapid recovery is the occurrence of quiet sleep, to interrupt the jactitation and delirium caused by atropine; in some few cases the administration of morphine has been followed by contraction of the mydriatic pupils,[3] and rapid relief has been afforded to the distressing ischuria.[4] Retardation of the pulse is also pretty generally noted, as in the case mentioned by Kohn and Koerner,[5] in which the pulse fell from 140 to 100, five minutes after subcutaneous injection of morphine. The frequency of the respiratory movements is also considerably diminished; Agnew[6] gives a case in

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[1] See the subject of Morphine Poisoning.

[2] Ueber den Antagonismus zwischen Opium u. Belladonna. Leipzig. 1869. pp. 13-18.

[3] For example, *Carroll Lee*, Americ. Journ. of Med. Science. Vol. 85. 1862. p. 57. In the case of a child six years of age, who had been poisoned with a drachm of succus belladonnæ, twenty drops of laudanum were given through the mouth, and an equal quantity per anum; after the third dose contraction of the pupil ensued, and after 120 drops complete recovery. *Bathurst Woodman* (Med. Times and Gaz. Oct. 8. 1864. p. 385) mentions a case, in which the pupils contracted under opium, but afterwards dilated again.

[4] *v. Graefe*, Arch. f. Ophthalmolog. IX. 2. p. 71. 1863.

[5] Berlin. klin. Wochenschr. II. 16. 1865.

[6] Pennsylvania Hosp. Rep. 1. p. 356. 1868.

which it sank from 30 to 19 in a minute. The difficulty in swallowing is also very much relieved. When the dose of atropine has been large, its effect will survive those of moderate doses of opium or morphine, so that when the opiate action ceases, the influence of the atropine again becomes manifest, and repeated doses of morphine, coup sur coup, may be necessary. In such a case, described by Abeille,[1] a boy six and a half years of age, who had taken three-quarters of a grain of atropine by mistake, and was found in profound stupor by the doctor, recovered slowly but completely by the gradual injection of morphine.

But, however highly we may estimate the value of opiates in atropine-poisoning, we must not forget that the most serious cases of poisoning have been cured even without morphine, and that excessive doses of the antidote will of course act deleteriously; lastly, it must be stated that morphine is not capable of averting death when very large doses of atropine have been taken.

We have yet to mention alcohol as a very common remedy in atropine-poisoning; Holthouse[2] gives a case in which it cured a child four years of age, who had been poisoned with from 3 to 4 grs. of atropine. That alcohol may be well borne in atropine-poisoning is proved by a case given by Castaldi,[3] in which a child six and a half months old took eleven and a half ounces of wine and recovered from poisoning, though opisthotonus had set in. It is needless to add that other remedies may be used according to the nature of the symptoms, such as the application of cold compresses to the head, cold douches, artificial respiration, alone or combined with electricity. Ambulatory treatment may be indicated by symptoms of sopor; it had a very favorable effect in a case mentioned by W. Legg[4]—Parsons[5] gives a similar case.

Bleeding, which has been recommended in various quarters, should be very rarely resorted to.

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[1] Gaz. méd. de Paris No. 43. Oct. 24, 1868.

[2] Med. Times and Gaz. Dec. 1859.

[3] Gaz. méd. d'Orient. IV. 5. 1860.

[4] Med. Times. Nov. 1866. p. 473.

[5] A Case of Belladonna Poisoning. Boston Med. and Surg. Journ. June 13, 1872.

Changes which Atropine undergoes in the Bodies of Men and Animals.

Atropine is very rapidly and completely absorbed by the mucous membrane of the stomach, so that in a few hours no alkaloid is to be found in this organ. Absorption by the small intestine is also very complete, yet most of the alkaloid relatively is found in it, since it is immediately secreted with the bile into the small intestine again, where it is again absorbed, so that no atropine or at most mere traces of it are found in the fæces. But absorption also takes place by the skin and conjunctiva. The atropine dropped upon the conjunctival membrane makes its way into the interior of the eye, and may be detected in the aqueous humor.[1] However quickly the poison passes into the blood, it is again very quickly and in an unchanged form secreted from it, especially by the urine. Thus Meuriot,[2] three hours after a small quantity of atropine had been given, found that all traces of it had disappeared from the urine. Schmidt[3] found no atropine remaining in the urine after ten hours, though one-fifth of a grain of atropine had been taken. Its entrance into the blood is, of course, most rapid in subcutaneous injection; dilatation of the pupil to its maximum was observed by Schmidt an hour after its internal administration, and by Taylor[4] fifteen minutes after, while Orfila observed the same effect within twelve minutes of its endermic administration. Atropine has been discovered unchanged in various organs of the body,[5] muscle, liver, blood, etc.

Tests for Atropine.

Strictly speaking, the only certain evidence we can have of the presence of atropine in organic substances (as, *e. g.*, matter

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[1] *de Ruyter*, Onderzoekingen, etc. Utrecht. 1853–54. VI.; and *Lemattre*, Arch. général. Juill. Août. p. 39 et seq 1865.

[2] De la méthode physiologique et de ses applicat. etc. Paris. 1868.

[3] Klin. Monatsschrift f. Augenheilkunde von Zehnder. 1864. p. 158.

[4] Treatise on Poisons, Deutsche Uebersetzung von Seydeler.

[5] *Puczniewsky*, De venenis præsertim Cantharidino, Strychnino, Atropino post intoxicationes in sanguine reperiendis. Dorpat. 1858; and *Dragendorff*, Ermittelung der Gifte und Beiträge u. s. w.

vomited, the blood, the contents of the stomach and intestines) is the extraction from them of a substance (not necessarily crystalline) which can be applied to the eye of the cat, and which produces upon it decidedly mydriatic effects. Very small quantities are sufficient for that purpose, whereas dogs, rabbits, etc., require much larger doses. This so-called physiological proof can, however, only establish beyond all doubt the existence of a mydriatic effect, while its more special characters cannot be determined. The examination of urine is of the highest importance in the recognition of atropine-poisoning. Allan,[1] Cohn, and Koerner,[2] found atropine in human urine, so did Harley[3] after the administration of $\frac{1}{36}$ of a grain. In many cases it is sufficient to instil the urine unaltered, in others it must be concentrated; but, for perfect security, the short and reliable method of Dragendorff[4] should be adopted. The urine is first acidulated with sulphuric acid, then immediately shaken twice with amylic alcohol, and then twice with ether; after the addition of ammonia to the fluid thus purified, the atropine can be immediately dissolved in ether, which, when evaporated, leaves the alkaloid behind in a condition in which it can be easily recognized.

The separation of atropine from organic substances is accomplished either according to the method of Stas and Otto, or according to that of Dragendorff. We digest the substances for several hours in water acidulated with sulphuric acid, then partially neutralize with magnesia, taking care that the fluid still remains distinctly acid; we next evaporate the fluid and digest for a long time in alcohol, acidulated with sulphuric acid, then distil off the ammonia and agitate with amylic alcohol, remove the alkaloid by means of acidulated water, again precipitate and dissolve it in fresh ether, or, better still, in chloroform. This generally leaves the atropine behind in a crystalline form. The residual product shows itself to be atropine by a series of reactions by no means very characteristic. The most valuable are

[1] Annal. der Chemie u. Physik. Bd. 84. p. 223.

[2] Berlin klin. Wochenschr. 1865. p. 162.

[3] Brit. Med. Journ. 1868. 28. March und 4. April.

[4] Beiträge zur gerichtl. Chemie einzelner organ. Gifte. 1872. St. Petersburg. p. 227.

the precipitates obtained by potassium-bismuth iodide and potassium-mercuric iodide, which, even when greatly diluted, will detect 1 : 4000.[1]

APPENDIX.

Poisoning with Hyoscyamus and Hyoscyamine.

Hyoscyamine ($C_{15}H_{17}NO$?) is found most abundantly in the seeds of Hyoscyamus niger and Hyoscyamus albus ; it was first obtained in a state of purity in 1833 by Geiger and Hesse ; according to their accounts it crystallizes slowly in stellate or fasciculate masses of silky and, for the most part, transparent acicular crystals ; it is free from odor, but has a very sharp and unpleasant taste. In the impure state it forms a tough, viscid brown substance, having a heavy, tobacco-like odor. Hyoscyamine is a true alkaloid, and forms, in combination with acids, salts which crystallize readily.

Poisoning has been frequently produced by mistaking hyoscyamus root for edible roots,[2] by taking medicines internally which were intended for outward application,[3] by taking overdoses of medicinal preparations,[4] and especially by eating henbane seeds.[5]

The symptoms so entirely correspond in every respect with those of atropine-poisoning, that we might consider both forms

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[1] For further particulars about precautions and methods of separating atropine from organized substances and other reactions, see :

Dragendorff, Ermittelung der Gifte. p. 278 ff.

The same, Beiträge u. s. w. p. 221 ff.

Husemann, Pflanzenstoffe. p. 436 ff.

[2] *Courtay*, Abeille méd. 1851.—*Zamboni*, Empoisonnement d'une famille par Racine de jusquiame. Moniteur des Hôpit. No. 20. 1876.

[3] *Deutsch*, Vergiftung durch Hyoscyamus und Conium. Preuss. med. Vereinszeitg. No. 9. 1851.

[4] *Cabot*, Urticaire par l'usage de la jusquiame. Americ. Journ. of Med. Sciences. Oct. 1851.

[5] *Danielli*, Bull. de Thérap. LXX. p. 285. Rczek, Allg. Wein. med. Zeitg. 30. 1864.

of poisoning under the same head. But Schroff's[1] assertion that hyoscyamine differs so far quantitatively from atropine, that it acts far more violently, especially on the pupils, which it dilates more rapidly, more completely, and for a longer period, necessitates a few words on the subject of poisoning by hyoscyamine. Most modern authors, however, are agreed that there is no such difference, and that the supposed difference may depend on the unequal purity of the preparations. Hyoscyamus is also said to produce sleep sooner than atropine, to act less powerfully on the sphincters of the anus and bladder, and to be not so constantly followed by the scarlet exanthem; yet we have instances recorded of this very symptom.

Schroff's view, that atropine and hyoscyamine are essentially identical in their action, is confirmed by the researches of Hellmann.[2] He has proved that even the products of decomposition of both alkaloids are similar in their action, and that hyoscinic acid is as inactive as tropaic acid. He also finds that hyoscine, like tropine, paralyzes the extremities of the vagus, retards respiration, etc., and that the action of hyoscyamine and atropine is identical. So that what has been said in reference to atropine, its action, symptoms, prognosis, treatment, etc., is directly applicable to Hyoscyamus niger and hyoscyamine.

Poisoning by Solanine and Plants containing it.

Solanine ($\text{Є}_{43}H_{69}N\Theta_{16}$), discovered by Defosses in 1820 in the berries of the black or garden nightshade (Solanum nigrum), is an alkaloid which is also found in the woody nightshade or bittersweet (Solanum dulcamara), in the fruit and shoots of the common potato (Solanum tuberosum), in susumber berries (Solanum bacciferum), etc. Solanine is mostly found in the young buds and green fruit of the potato; it also exists in unripe and

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[1] Ueber Hyoscyamus, u. s. w. Wochenblatt der Zeitschrift Wiener Aerztc. 1855; and earlier, Zeitschr. d. Gesellsch. der Aerzte zu Wien. 1852. pp. 211–242.

[2] Beiträge zur Kenntniss der physiologischen Wirkung des Hyoscyamins und der Spaltungsprodukte des Hyoscyamins und des Atropins. Jena. 1873.

diseased potatoes. It crystallizes in very small white prisms, glistening like mother-of-pearl, but it is generally sold as an amorphous white powder; it is soluble in 500 parts of alcohol and 8,000 parts of boiling water.

Etiology.

Poisoning by solanine is not uncommon. For instance, there is a case on record of a boy four years of age,[1] who, with some other children, ate bittersweet berries; he died, but the others recovered. A girl of fourteen[2] died from eating green potato-apples. Slighter cases of poisoning by black nightshade are described by Magne[3] and Maury;[4] Manners[5] tells of a whole family in Jamaica poisoned by eating fish together with susumber berries. Barthez, in Paris,[6] saw a boy poisoned by "Jerusalem cherries" (berries of Solanum pseudo-capsicum). In a case reported by Bourneville[7] ten bittersweet berries sufficed to produce violent symptoms of poisoning in a child eleven years of age.

Symptoms and Course.

The symptoms which are produced by these different forms of solanine are not alike in all cases, because the action of solanine is modified by that of other substances combined with it. As far as I know there are no cases of poisoning by pure solanine, therefore we must confine ourselves to the symptoms observed after poisoning by the plants belonging to this tribe. After partaking of unripe, sprouting, or diseased potatoes, or potato-apples, the first symptoms usually observed are vomiting,

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[1] Accidental Poisoning by the Berries of Woody Nightshade. The Lancet. June, 1856.

[2] *Th. Morris*, Brit. Med. Journ. Sept. 3, 1859.

[3] Gazette des Hôpit. 112. 1859.

[4] Gazette des Hôpit. 35. 1864.

[5] Edinburgh Med. Journ. Nov. 398. 1867.

[6] Compare *Chatin*, Journ. de Chim. méd. Janvr. 20. 1869.

[7] Gaz. de Hôpit. 35. 1854.

then restlessness, cold damp skin, quick and labored breathing, frequent and weak pulse, anxiety of countenance, and usually dilatation of the pupils, not, however, to any great extent; occasionally the general restlessness is interrupted by a sleep of short duration. Very often diarrhœa sets in, the stools containing undigested fragments of potato, etc., and if the diarrhœa and vomiting last long, as in a case described by Munke,[1] a typical form of cholera may be developed, with cramp of the calf of the leg, aphonia, facies hippocratica, etc. In many cases of poisoning by potatoes, gastro-enteritic symptoms, with pain and tenderness of the epigastric and hypochondriac regions, are present. At the same time, as in several cases mentioned by O'Brien,[2] there has been observed erysipelatous swelling of the face, with the formation of bullæ or œdema of the eyelids, or reddening of the whole face, together with severe muscular and articular pain. In one case reported by this author an exanthem appeared and again disappeared frequently in the course of the day. With regard to the nervous centres, we may have disturbed consciousness, fainting-fits, etc.; these symptoms may continue for some time; death is preceded by gradual retardation of the breathing, violent dyspnœa, and irregular and feeble cardiac pulsation. M'Cormack[3] reports the breaking out of land-scurvy among a poor working population from eating a great quantity of diseased potatoes, but as in this instance all their other resources in the way of nourishment were very wretched, it is doubtful if we ought to regard this as a case of chronic poisoning by solanine. The symptoms of bittersweet-poisoning appeared in a few cases: as, *e. g.*, difficulty in swallowing and speaking, convulsive movements of the limbs, and actual convulsions. In the case reported by Bourneville catalepsy was observed. Vomiting, a quick and feeble pulse, difficulty of breathing, and dilatation of the pupils are among the regular symptoms, though the last is reported to be absent in individual cases. Similar symptoms are observed

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[1] Ein Fall von Vergiftung durch den Genuss unreifer Kartoffel. Med. Annal. 11 Bd. 2 Heft. 1845.

[2] Form of Gastro-Enteritis Caused by Diseased Potatoes London Med. Gaz. March, 1846.

[3] On Land-Scurvy Produced by Eating Diseased Potatoes. The Lancet. July, 1846.

in poisoning by the berries or leaves of the black nightshade and by susumber berries: carphology, tympanites, great restlessness, delirium and hallucinations, dilatation of the pupils, cramps, etc.

Analysis of Symptoms. Nature of Solanine-Poisoning.

But few investigators had, till quite lately, made any experiments with solanine; and the results of their experiments were widely at variance. In the first place, it has been noticed that some animals, swine, for instance, as Fraas[1] has shown, enjoy a kind of immunity from this poison. Then it is important to remember that the solanine of commerce is often adulterated with a considerable amount of solanidine; we must also, as Husemann[2] suggests, bear in mind the possibility that solanine may readily separate in the stomach of animals and human beings into sugar and solanidine, so that even when pure solanine is given, its effects may be complicated with those of solanidine. Husemann's work is specially calculated to explain and reconcile the contradictions which are found in the works of Clarus,[3] Schroff,[4] Leydorff,[5] Fronmueller,[6] and Leonidas van Praag.[7] Husemann shows that although the effects of solanine and solanidine are in some points identical, yet there are essential differences in their action. In general solanine and solanidine when given to animals produce first a stage of apathy, manifested by indisposition to voluntary movements and diminished sensibility to outward impressions, not so much with regard to those of mere contact as to those which are painful. Slight muscular trembling, especially in the muscles of mastication, accompanies this state; respiration is at first much accelerated, afterwards much retarded; the pulse is irregular, and bears no

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[1] Ueber Solaninvergiftung. Virch. Arch. VII. Bd. pp. 225–227. 1854.

[2] Ueber die Wirkung des Solanins u. Solanidins. Arch. f. experiment. Pathologie. u. Pharmakologie. IV. Bd. 1875. pp. 309–339.

[3] Reil's Journal für Pharmacodynamik. I. 2 Heft. 1857.

[4] Pharmacologie. 1 Aufl. p. 552.

[5] Studien über den Einfluss des Solanins auf Thiere und Menschen. Marburg. 1863.

[6] Deutsche Klinik. 40. 1865.

[7] Journal für Pharmacodynamik. I. 2. 1857. p. 275.

relation to the respirations. After this stage has lasted some time, a greater or less degree of cyanosis sets in, the animal falls suddenly forward, and passes into a state of convulsions, which soon ends in death. Husemann considers that paralysis of the motor centres is the cause of the first stage, and that carbonic acid poisoning is the cause of the convulsions and death. Clarus attributes the retardation of respiration to paralysis of the medulla oblongata, and the irregularity of cardiac action to the influence of the poison on the vagus.

So far the effects of both poisons coincide. But a difference between them soon appears in their action on the eye. Both, when directly applied to the conjunctiva, cause redness with increased secretion, solanidine causing more irritation than solanine, but the effects which they produce upon the pupil are unlike; solanine leaves the pupil unaltered, at most contracting it for a short time by local irritation; whereas a very perceptible mydriasis is one of the first effects of the action of solanidine. An essential difference is observed in the manner in which the two substances affect the temperature of the body.

Whereas pure solanine often lowers the temperature by 5.4° Fahr., solanidine raises it by 3.6° Fahr., or over. The vomiting which accompanies ordinary solanine-poisoning is regarded by some as reflex, and set up by irritation of the sensitive nerves of the stomach by the poison; this may perhaps be the case with solanidine: but Th. Husemann is probably more correct in looking upon the vomiting as cerebral, and produced by the action of solanine on the brain, and especially on the vomitive centre. That the brain is really sympathetically affected by these poisons is sufficiently proved by Schroff's experiments on himself, in which giddiness, heaviness of the head, trouble of the sensorium, and tendency to sleep were amongst the symptoms. Solanine and solanidine, however, do not really act as narcotics, for those who experimented on themselves, although they felt drowsy, could not go to sleep, and Fronmueller in his clinical practice failed to induce sleep even by large doses (from three to nearly four grains) of solanine.

The main action of solanine consists, then, in paralysis of the motor centre and of the respiratory centre, and so causes death

by asphyxia. The foregoing considerations afford an explanation of the symptoms which have been observed in poisoning by plants containing solanine—the vomiting, the collapse, the death. But the diarrhœa, so constantly observed in these cases, remains unexplained. We may consider it highly probable that this effect is not due to the action of the solanine itself, but is rather the consequence of the venous engorgement (der Cyanose), which exists also in the intestinal mucous membrane; it may also be due, in part, to the mechanical and chemical irritation set up by the presence in the alimentary canal of the poisonous ingesta or the products of their decomposition. It is obvious that the great drain of fluid caused by the vomiting and diarrhœa contributes, together with the paralysis of the nerve-centre, to bring about a fatal result.

Diagnosis and Differential Diagnosis.

The recognition of poisoning by plants and portions of plants containing solanine, rests mainly on the history of the case, and on the presence of portions of such plants in the matter vomited and in the fæces. In the absence of these evidences, it will be almost impossible to recognize solanine-poisoning as such, for it will be very difficult to distinguish it from a simple attack of vomiting and diarrhœa, or an attack of cholera, especially as this poison has no characteristic symptoms, and even dilatation of the pupils is not constant.

Prognosis.

Poisoning by solanine does not, in general, end fatally, the vomiting—which is one of the results of the poison—contributing to its elimination.

Results of Autopsies.

In autopsies which have been performed on animals, no particular changes have been discovered, except vascular engorgement of the brain and its membranes; in most cases death

appears to have been due to asphyxia, or to the excessive drain of fluid.

Treatment.

The most important part of the treatment is to administer emetics and aperients, so as to promote the removal of the poison and the poisonous vegetable matters from the alimentary canal. It is scarcely necessary to say that we must combine appropriate stimulating remedies with these other measures—ether, mustard poultices, etc., when they are called for by the predominant symptoms.

Changes which Solanine undergoes in the Bodies of Animals.—Tests.

No accurate accounts exist at present as to the changes which solanine undergoes in the body: a chemical test sufficient for judicial purposes, according to Husemann,[1] is founded on the fact that solanine is not precipitated from an acid or alkaline solution by benzine, chloroform, or petroleum ether, while it is readily separated from an alkaline solution by hot amylic alcohol—a property which is peculiar to it and morphine, from which it can easily be distinguished; further, on this fact, among others, that solanine, when treated with hydrochloric acid, is converted into solanidine and sugar, both soluble in ether, while hydrochlorate of morphia is insoluble in ether.

Poisoning by Physostigmine (Eserine), $C_{15}H_{21}N_3O_2$.—Calabar Bean.

According to Hesse physostigmine forms a colorless varnish, which readily dries into a brittle mass, whereas, according to Vée, when in a pure condition, it forms crystalline crusts or small shiny rhomboidal plates; it is tasteless, strongly alkaline,

[1] Die Pflanzenstoffe. p. 426.

sparingly soluble in water, but readily so in alcohol, ether, chloroform, benzol, and sulphide of carbon.[1]

Physostigmine is the alkaloid and active principle of the calabar bean. Cases of poisoning by this bean are very rare, but some have been observed.

Etiology.

The poisonous properties of the bean, as we learn from different travellers and missionaries, are very frequently utilized in its native country, the west coast of Africa, for the so-called judgment of God, to convict magicians, criminals, etc.; those that succumb are pronounced guilty, and those that recover, by vomiting, are acquitted.

Cameron[2] observed forty-six cases of poisoning with calabar bean, arising from the circumstance that some of these beans, which had been brought in a ship from the west coast of Africa to Liverpool, were found and eaten by children. Such cases seem to be not infrequent in seaports, for Linden,[3] of St. Petersburg, reports that a boy was poisoned in the same way by a bean found in the harbor. David Young[4] also mentions the poisoning of two boys who had eaten pieces of calabar bean. Fraser[5] gives an account of two maid-servants who were poisoned by tasting some of the embryos of the bean from curiosity. As to the quantity which is sufficient to poison, small pieces of the bean and small fractions of a grain of the alkaloid seem to have produced very serious symptoms. In an experiment by Fronmueller,[6] one-sixth of a grain caused, in the course of an hour, nausea, dimness of vision, and slight myosis. In the African ordeals, from one to twenty-five beans in powder are given, equal to from one drachm to over three ounces; but it would seem

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[1] Comp. *Husemann*, Die Pflanzenstoffe. p. 68.

[2] *J. K. Evans*, Med. Times and Gaz. Oct. 15. p. 406. 1864.

[3] Gaz. hebdom. No. 39. p. 641. 1864.

[4] Edinb. Med. Journ. Aug. p. 192. 1864.

[5] On the Therapeutic Action of the Calabar Bean. Edinb. Med. Jour. July, Aug. and Sep. 1863.

[6] Deutsche Klinik. No. 35. 1864.

that the chance of death is not in direct proportion to the quantity of the dose. Four and a half grains of the extract of the calabar bean sufficed to kill a rabbit. The maximum doses prescribed in the German Pharmacopœia are three-tenths of a grain per dose, and a little less than a grain per day.

Symptoms and Course.

The symptoms of poisoning generally show themselves soon after the introduction of the poison; with large doses they set in almost suddenly after from five to ten minutes, with smaller ones usually after from twenty to thirty minutes, but sometimes not till after two and a half hours. These statements are taken from Evans's report. African travellers are tolerably unanimous in their description of the symptoms which this poison produces. They are: violent thirst, inability to swallow, cramps, and twitchings in various muscles; there is no loss of consciousness or of speech till shortly before death, which supervenes in about half an hour. Sometimes, especially when very large quantities of the bean are given, vomiting comes on pretty soon: this eliminates the poison, and complete recovery ensues rapidly. Slight headache may remain for a short time after.

This general and superficial description of symptoms has been supplemented by Fraser's experiments on himself, and by his observation of the cases already mentioned. In Fraser's experiments on himself, five minutes after the introduction of the poison, he felt pain in the epigastrium under the sternum, at first slight, but becoming very violent later on; this was followed soon after by eructation and a sense of shortness of breath; subsequently giddiness and weakness of the muscles of the extremities supervened. When he took larger doses, he was seized with cramp of the muscles of the chest, an increase of the giddiness, disturbance of vision, increased flow of saliva, and perspiration; cardiac action was often retarded, whereas in a case of Christison's it was very disturbed and irregular.

In the forty-six cases communicated by Evans, the chief symptom observed was a very marked degree of muscular weakness, almost amounting to paralysis, which lasted thirty-six hours in

cases which recovered ultimately. The second prominent symptom was decided collapse with pinched countenance, cold clammy extremities, cold perspiration, and a weak and slow pulse. All the forty-six patients, with only one exception, were seized with vomiting or great nausea; diarrhœa occurred in fifteen cases; pain and uneasiness in the stomach in all. There were no convulsions or loss of consciousness in any case; nor was myosis present in every case.

Analysis of Symptoms—Nature of Calabar Poisoning.

There is no poison concerning the action of which physiological researches give such diametrically opposite accounts, as of calabar bean. We are not, therefore, in a position at present to pronounce how physostigmine causes death. Some investigators assert that its action resembles that of curare, paralyzing the peripheral extremities of the nerves of the voluntary muscles, and so producing a fatal result, while others declare that it primarily paralyzes the spinal marrow, and so leads to paralysis of respiration. We must admit that changes have been observed in the striped muscles similar to those produced by curare. For instance, Fraser[1] observed that the muscles became paralyzed after he had noticed some transient convulsive fibrillar movements; it has also been observed in frogs, that while the muscles still react to direct irritation, they cannot be excited to contraction through their nerves; this certainly resembles the effect of curare.

Still it is more than doubtful whether this is the main cause of death in calabar-poisoning, because some very decisive experiments point unmistakably to a primary central paralysis of the spinal marrow. The most important of these are Laschkewich's[2] experiments, which show that in frogs the extremities, which had been severed from connection with the vascular system before the poisoning, were quite as much acted upon by the poison as those whose arteries had been left intact; and, further, a series of ex-

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[1] Transactions of the Royal Society of Edinburgh. XXIV. 1867.
[2] Arch. f. pathol. Anatom. XXXV. 291.

periments undertaken by Fraser,[1] Roeber,[2] Laschkewich,[3] Dor,[4] Tachau,[5] and others, which establish a diminution and ultimately a complete cessation of reflex excitability, corroborate the idea of a central paralysis. That this central paralysis precedes the paralysis of the peripheral extremities of the muscular nerves, is proved by the fact that, in warm-blooded animals who died of the calabar poison, contraction of the muscles could be excited immediately after death by irritation of the nerves. In general, this paralysis is not preceded by convulsions, and Vintschgau's[6] statement that he has occasionally observed tetanic symptoms in cold-blooded animals, stands alone and unsupported in the face of a considerable series of contrary observations. In warm-blooded animals, however, convulsions are frequently observed, but it is highly probable that they are dependent on the carbonic acid poisoning which accompanies death from asphyxia or from cardiac paralysis.

The respiratory process is the first to suffer from this action of the poison upon the spinal marrow and the motor nerves: according to the reports of v. Bezold and Goetz[7] respiration is accelerated in the early stage of the poisoning from peripheral irritation of the vagus, but, soon after, the number and intensity of the respirations diminish till they cease altogether.

Physostigmine is, however, a not ineffective cardiac poison. Later investigators are unanimously agreed that the number and intensity of cardiac contractions diminish considerably under the influence of the alkaloid; some of them, as, for instance, Tachau

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[1] On the Characters, etc., of the Ordeal Bean of Calabar. Edinb. Med. Journ. Vol. IX. 1864.

[2] Ueber die Wirkungen des Calabarextractes auf Herz und Rueckenmark. Dissert. Berlin. 1868.

[3] Beobachtungen über die physiolog. Wirkungen der Calabarbohne. Virch. Arch. XXXV. p. 291 ff.

[4] Études physiologiques sur la fève de calabar. Arch. des scienc., phys. et natur. Nouv. Per. T. XVIII. Genève. 1863. pp. 330-343.

[5] Versuche über die Wirkung des Calabarbohnenextractes. Arch. f. Heilkunde. 1865. pp. 69-78.

[6] Sitzungberichte der Wiener Academie. Mathemat. naturwissensch. Classe. Abthl. LV. 49.

[7] *Gscheidlen*, Untersuchung. a. d. physiol. Laborator. zu Würzburg. II. 263 ff.

(in the case of rabbits) and Roeber,[1] attribute this diminution to diminished irritability of the excito-motor cardiac nerve-centres; others, on the contrary, as, for example, Laschkewich, Lenz,[2] trace the retardation to irritation of the inhibitory apparatus of the heart, not, however, through the vagus, but through the sympathetic ganglia within the heart. That the vagus is not excited by calabar, either at its origin or at its termination in the heart, had been already proved by Roeber[3] by experiments on frogs, in which he observed, both in the cases of curarized and nicotinized frogs and rabbits, that even after section of the vagus the number of cardiac pulsations gradually decreased. From all the observations which have been made it would appear that death from calabar-poisoning is primarily due to paralysis of respiration, and not to the action of physostigmine on the heart. For, according to the reports of Bauer,[4] v. Bezold and Goetz, Arnstein and Sustschinsky,[5] Westermann,[6] retardation of cardiac action was not a prominent symptom, and the effects of the action of the poison on the heart could easily be arrested by artificial respiration; moreover, the heart of dying animals was found to beat strongly up to the moment of death.[7]

No explanation has hitherto been forthcoming of Boehm's experiments on the frog's heart, the results of which were contradictory to most of the statements put forward as to the action of the calabar poison on the vagus, for, according to Boehm,[8] physostigmine exercises the same paralyzing effect on the extremities of the vagus as atropine. Rossbach and Froehlich[9] conclude from their experiments on the hearts of frogs that (at

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[1] Loc. cit. pp. 54 and 36, 37.

[2] Versuche über die Einwirkung der Calabarbohne auf dem Blutkreislauf. Dissert. Zürich. 1864. p. 30.

[3] Loc. cit. pp. 29, 30, 31.

[4] Centralbl. f. d. med. Wissenschaften. 1866. 577.

[5] Untersuchungen aus d. phys. Laborat. zu Würzburg. II. 81.

[6] Untersuchungen über d. Wirkungen d. Calabarbohne. Diss. Dorpat. 1867.

[7] See Hermann, Experiment. Toxikologie. p. 340.

[8] Studien über Herzgifte. Würzburg. 1871. p. 80 ff.

[9] Untersuchungen über die physiologischen Wirkungen des Atropin und Physostigmin auf Pupille und Herz. Pharmacolog. Uuntersuchungen von *Rossbach.* 1 Bd. 1 Heft. p. 56 ff. Würzburg. 1873.

least in one series of frogs) the first symptom of the action of the poison on the heart is a retardation of the cardiac pulsations, with increased intensity of each contraction, and that this retardation of the pulsations is the result of excitement of the inhibitory centres within the heart, and, as a proof of this, it was observed that a very slight irritation of the venous sinus and auricles arrested the diastolic movement.

It is remarkable that irritation of the vagus produced no effect whatever; therefore paralysis of the vagus must have coincided with irritation of the inhibitory centres in the heart. Another symptom noticed by the above-mentioned investigators was excitement of the motor-cardiac centres, which excitement eventually gave place to general cardiac paralysis. The excitor (accelerative) nerves of the heart are not affected by physostigmine, but the blood-vessels undergo distinct changes. v. Bezold and Goetz observed a marked contraction of the vessels, and this narrowing was succeeded by dilatation. This irritation followed by paralysis points to the action of the poison on the vaso-motor centre. According to the experiments of these authors the blood-pressure is increased in the early stage of the poisoning, whereas Lenz's[1] experiments on the blood-pressure in dogs tended to show a diminution of pressure as the main result. This change in the blood-pressure is easily accounted for by the contraction of the vessels, and it is further explained, at least partially, *i. e.*, as regards the increase, by the contraction of the intestinal canal and its vessels. For, according to the researches of Bauer (l. c.) and Westermann (l. c.), the calabar poison produces an actual tetanus of the intestines, which depends upon a direct influence on the intestine itself, since this effect is not observed when the flow of blood to the intestine is arrested. It will even sometimes happen that when calabar poison is injected into one of the arteries of the small intestine, only that portion of the intestine connected with the vessel is thrown into tetanic convulsions. A similar localization of the contractions takes place when calabar extract is conveyed into a ligatured portion

[1] Versuche über die Einwirkung der Calabarbohne auf den Blutkreislauf Zurich. 1864. p. 27. Dissert.

of intestine. Other organs, also composed of smooth muscle-fibres—the uterus, ureter, sphincter of the bladder, and spleen—exhibit contractions of their involuntary muscular elements (Bauer). When this tetanic condition of the intestine extends along the whole alimentary canal, as is usually the case when the action of physostigmine becomes general, the extremities of the intestinal vessels are compressed, and this is a further cause of the increased blood-pressure. The increased flow of saliva observed in almost all poisoning cases (the cutaneous and lachrymal secretions are also promoted) is attributed by Heidenhain[1] to a central irritation of the secretory nerves, as it failed to occur after section of the chorda near the submaxillary gland. Heidenhain's experiments showed that the flow of blood through the submaxillary gland was retarded by moderate doses, and completely arrested by large ones, evidently from contraction of the vessels. Rossbach[2] confirms this, though he at the same time characterizes Heidenhain's theory of an antagonism existing between atropine and physostigmine as "one-sided."

The action of calabar bean on the iris requires special mention. Local application of the poison to the conjunctiva causes considerable contraction of the pupil, and this contraction is accompanied with loss of focalizing power. Myosis comes on soon after the dropping-in of the poison, *i. e.*, in twelve to fifteen minutes, and reaches its climax[3] rapidly within from five to ten minutes, remaining at this point for from six to eighteen hours, and disappearing after two or three days. It is a question whether the contraction of the pupil is caused by paralysis of the dilatator, as Fraser, Hirschmann,[4] Bernstein and Dogiel[5] assume, or by stronger contraction of the sphincter, as is maintained by Gruenhagen and Rogow,[6] v. Bezold and Goetz, and

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[1] Pflueger's Archiv für die gesammte Physiologie. V. 40. Ueber die Wirkungen einiger Gifte auf die Nerven der Glandula submaxillaris.

[2] Pharmacolog. Untersuchungen. 1 Bd. 4. Heft. p. 239. 1874. Der Antagonismus in d. Wirkung des Atropins u. Physostigmins auf die Speichelsecretion, etc.

[3] See *Hermann*, Toxikologie. p. 342.

[4] Archiv f. Anat. u. Physiol. 1863. p. 309.

[5] Verhandlungen d. n. h. med. Vereins zu Heidelberg. IV. 2. 1865.

[6] Zeitschrift f. rationelle Medic. 3. Serie. XXIX. 1; und Centralblatt f. die med. Wissenschaften. 1863. 577.

Engelhardt.[1] The latter view is corroborated by the fact that the effect of calabar is easily neutralized by atropine; whereas contraction of the atropinized pupil is not so easily effected by calabar.[2] Then, again, the contraction of the pupil by calabar is too considerable to be produced by simple paralysis of the sympathetic.

Engelhardt's statement, that direct local electric irritation of an eye which has been treated with calabar causes dilatation of the pupil, may be explained by the consideration that the electric excitement acts upon both sphincter and dilatator, but the former, being already contracted to its utmost capability by calabar, cannot be further contracted; whereas the dilatator can be acted upon by the shock. Rossbach[3] states, and supports his statement by experiments on rabbits and frogs, that small doses of physostigmine contract the pupils, but very large doses dilate them as atropine does; therefore he concludes that only a quantitative difference exists in the action of these two poisons, regarded by some as antagonistic. Graefe[4] also attributes the action of calabar solely to irritation of the sphincter.

We conclude, then, that, according to our present information on the subject, *the special character of calabar-poisoning consists mainly in a diminution of the excitability or complete paralysis of the locomotor centres, situated in the medulla spinalis, in paralysis of the excito-motor cardiac centres and their peripheral extremities; also in producing contraction of the vessels and of the unstriped muscles, especially those of the intestine and the sphincter iridis, as well as in promoting salivary and other secretions.*

Results of Autopsies.

We have but very few reports of autopsies performed on persons who have been poisoned by calabar. In the Cameron-

[1] Untersuchungen aus d. physiol. Laborat in Würzburg. II. 297.

[2] *Harnack*, Archiv für experimentelle Pathologie u. Pharmakologie. II. Band. p. 307, maintains, however, on the strength of accurate experiments, that even in an atropinized eye the pupil was contracted ad minimum by pure physostigmine.

[3] Loc. cit. p. 14. I. Bd. 1. Heft.

[4] Deutsche Klinik. 16. 1861.

Evans case the most important point observed was that the left side of the heart was very much distended, and the whole heart filled with blood, partly fluid, partly coagulated. The same result is found in most reports of dissections of poisoned animals; but in these, evidences are sometimes found of slight gastro-enteritis.

Diagnosis and Differential Diagnosis.

The diagnosis of physostigmine-poisoning may be very difficult if there is no history to help us. It must rest upon the existence of great general loss of power, together with contracted pupils and an undisturbed sensorium. In such a case it is hard to decide between calabar-poisoning and poisoning by curare or conium; the myotic condition of the pupils affords the greatest assistance.

Prognosis.

The prognosis of calabar-poisoning is favorable if vomiting comes on at an early stage, and if there is a rapid elimination of the poison. Of the forty-six cases given by Cameron and Evans only one, a boy six years of age, died; the rest recovered pretty rapidly. Recovery is generally complete; only in a few cases some muscular weakness, more or less pronounced, remains.

Treatment.

It follows from what has been said that our treatment must, in the first place, be directed to emptying the stomach by means of emetics or the stomach-pump. Further on in the case threatened asphyxia must be averted by artificial respiration and threatened cardiac paralysis by the use of stimulants, such as subcutaneous injections of ether or camphorated oil. Under some circumstances it may be necessary to maintain the heat of the body by the application of warm poultices and warm coverings, and by irritation of the skin. In poisonings in the human subject no therapeutic use has hitherto been made of atropine, which seems, *a priori*, calculated to act as an antidote, although

it may be accepted as a fact that atropine is capable of counteracting most of the effects of physostigmine.

Changes which Physostigmine undergoes in the Bodies of Animals.

Physostigmine passes from the mucous membrane of the stomach, as well as from the subcutaneous connective tissue, into the underlying tissues of the body, and is carried in the circulating fluid to all the organs of the body, so that, as the experiments of Laborde and Léven[1] prove, the blood of poisoned animals will intoxicate others. According to Pander's[2] experiments the poison very quickly passes into the saliva, is found in the bile, and passes with it into the intestine; he succeeded in finding the alkaloid in the blood, the liver, the stomach, and the small intestine. He could not detect it in the urine; it is, therefore, doubtful whether the poison is secreted by the kidneys, or whether it may not be destroyed in the body; it does not resist putrefaction.

Chemical and Physiological Tests of Physostigmine.

The chief defect in the chemical test is that physostigmine gives no quite characteristic reaction; the most valuable means for recognizing it, according to Pander[3] and Dragendorff, is bromine-water, which gives to a solution of physostigmine in sulphuric acid, even when diluted 10,000 times, a reddish-brown color, and so enables us to detect even one-thirteen-hundredth of a grain (one-twentieth of a milligramme) of the poison. If, on the other hand, the solution of physostigmine be added to the bromine-water, a yellowish precipitate is thrown down with a little less than one-six-hundredth of a grain of the poison. The separation of the alkaloid from organic substances is effected by means of benzine, according to Dragendorff's method. The

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[1] Gaz. méd. de Paris. 3. 1870.

[2] Beiträge zum gerichtlich chemischen Nachweis des Brucins, Emetins und Physostigmins in thierischen Flüssigkeiten u. Geweben. Dissert. Dorpat. 1871.

[3] Loc. cit. und *Dragendorff*, Ermittel. d. Gifte. p. 292 ff. u. Beiträge, etc. 215 ff.

substance so obtained has the property of causing decided contraction of the pupil in rabbits and guinea-pigs, when only one-one-hundredth of a milligramme (a little over one-seven-thousandth of a grain) of the alkaloid is introduced into the conjunctiva. This so-called physiological test is perhaps the most important in testing for physostigmine. In cases of poisoning in human subjects Edwards succeeded (in the Cameron-Evans case already mentioned) in detecting physostigmine in the stomach and intestine ; he obtained an extract which produced contraction of the pupil in rabbits and produced death by syncope in frogs and mice.

Poisoning with Digitalis.

The purple foxglove, Digitalis purpurea, contains poisonous substances in all its parts, which must be regarded as glucosides, and which were formerly considered as one substance under the name of "digitalin." Homolle[1] was the first to exhibit from the leaves of the digitalis a poisonous substance, which was distinguished by the name of French digitalin ; this was also exhibited by Quevenne ; it consists of small white flakes, of a bitter taste, sparingly soluble in water, readily so in alcohol and acetic acid. Walz[2] exhibited a so-called German digitalin — a yellowish, uncrystallizable powder, readily soluble in cold and warm water. Other sorts of digitalin have been exhibited by Kosmann, Lancelot, Lebourdais, etc. Most of these investigators were aware that their digitalin was not a pure body, but consisted of several substances. Homolle especially tried to separate these from one another, but did not succeed, although he obtained four different substances from his digitalin, but these he could not obtain quite pure.

Nativelle[3] was the first to throw more light upon the chaos

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[1] Physiological and Chemical Action of the Bitter Principle of Digitalis. The Chemic. Gaz. Feb. 1845.

[2] Jahrb. Pharm. XII. 83. XIV. 20. u. s. w.

[3] Journ. chim. méd. XXI. 61. Monit. scientif. 1867. und N. Jahrb. Pharm. XXVII. 161. Journ. Pharm. (4) IX. 255.

of the various kinds of digitalin and their derivatives by exhibiting an active body in a crystalline form, digitalin (called by Nativelle, digitaleïn); secondly, an amorphous body, of a bitter taste, and also having active properties, digitaleïn (called by Nativelle, digitalin); and thirdly, another crystalline body, tasteless and inactive, which he named inert crystalline substance. But according to the researches of Schmiedeberg,[1] the crystallized digitalin is by no means a pure substance, but a compound of various active and inactive bodies, part of which exist in the plant, Digitalis purpurea, and part are products of the decomposition of digitalis. According to Schmiedeberg, there are four main substances, which are pharmacologically active, and produce the effect of digitalis:

1. *Digitonine*, which has a great resemblance to saponin in its qualities and action.

2. *Digitalin*,[2] which is insoluble in water, and forms the chief ingredient in the digitalin of Homolle and Quevenne.

3. *Digitaleïn*, which is distinguished by its ready solubility in water, and has the same action mainly as the German digitalin; and,

4. *Digitoxine*, which is the most powerful agent of all, and which forms the chief part of Nativelle's crystalline digitalin.

1. Digitonine, when heated with greatly diluted mineral acids, separates into sugar and two insoluble bodies, incapable of crystallization, of which one is called *digitoresine*, the other *digitoneïne:* therefore it is a true glucoside. Digitoneïne, again, is a glucoside, and when separated gives as a product *digitogenine*.

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[1] Untersuchungen über die pharmacologisch wirksamen Bestandtheile der Digitalis purpurea L Archiv f. experiment. Patholog. u. Pharmakologie. 1874 III. Bd. 1. Heft. p. 16 ff.

[2] *Robert Koppe* has subjected the action of digitoxine, digitalin. and digitaleïn to a searching investigation under the direction of Schmiedeberg, and by experiments partly on himself, partly on animals, has come to the conclusion that the qualitative action of these three substances is identical with each other, and with the mother-plant, but that there are quantitative differences. For details, we must refer to the original Untersuchungen über die pharmacologischen Wirkungen des Digitoxins, Digitalins, und Digitaleïns. Dissert. Dorpat. 1874. u Arch. f. experiment. Patholog. u. Pharmakologie. III. Bd. 1874. p. 275 ff.

Digitonine again, under other circumstances, separates into digitoneïne and *paradigitonine*.

2. Digitalin is also a glucoside, and when heated with very weak mineral acids, separates into glucose and a resinous substance, *digitaliresine.*

3. Digitaleïn under like circumstances separates into the same products as digitalis.

4. Digitoxine, when the alcoholic solution is heated with very much diluted mineral acids, passes into *toxiresine.*[1]

The different kinds offered for sale, which have different properties according to the manufactory from which they issue, contain the four bodies above-mentioned, and the products of their decomposition, with other inactive ingredients in different proportions, and differ accordingly in their quantitative effect, though they are qualitatively like one another and the mother-plant and the various pharmaceutic preparations.

Etiology.

Poisoning with digitalis is not very frequent, but it does occur sometimes under very various circumstances, and the series of symptoms presented give it not only a pharmacological and physiological, but also a toxicological interest. Poisoning may occur with the fresh plant, as shown in the case communicated by Severin Caussé,[2] in which a young woman, twenty-seven years of age, after drinking the freshly expressed juice of digitalis leaves, became violently ill, and died the thirteenth day after the poisoning.

Poisoning has also frequently occurred from mistaking the leaves for those of other plants, as in the case mentioned by Mazel,[3] in which an apothecary's maid-servant, twenty-five years of age, prepared herself an infusion of not quite two drachms of

[1] *Dr. Perier* has investigated the action of toxiresine and digitaliresine on the animal organism. The details have no important bearing on our subject, and may be consulted in the original. Archiv f. experimen. Patholog. u. Pharmakologie. IV. Bd. 1875 p. 191 ff.

[2] Annal. d'Hygiène. 2. Ser. XI. Avril, 1859.

[3] Gaz. des Hôpit. 74. 1864.

digitalis leaves (instead of borage leaves), and died in five days. Poisoning has also occurred from Homolle's digitalin; thus Leroux[1] relates that a man seventy-two years of age took twice, in the course of a few hours, nearly half a grain of digitalin, became very violently ill, and recovered very slowly. Digitalis has also been used for criminal poisoning; for example, in 1864, a Parisian doctor, De la Pommerais, poisoned a woman named de Paw.

Slighter cases of poisoning with digitalis and its preparations occur frequently enough in medical practice, as when patients with heart disease are trusted with strong preparations of digitalis, or when they continue to take weaker preparations for a long time.

As to the dose which may lead to poisoning, it is very difficult to fix it precisely, because the preparations differ so much in the amount of active ingredients which they contain. The German Pharmacopœia fixes fifteen grains (one gramme) per diem as the maximum dose of digitalis leaves—twelve grains of extract of digitalis; while of the German digitalin commonly sold one-fifth of a grain (0.012) is given as the maximum dose; decided effects are produced by one-thirtieth of a grain (0.002) of Homolle's digitalin. Of the tincture of digitalis the maximum dose is a drachm and a half per diem. Of Nativelle's digitalin as much as one-tenth of a grain per diem may be given.

Symptomatology and Course.

Digitalis and its derivatives have an unpleasantly bitter taste, and create a sensation of nausea, sickness, tendency to vomit, and actual vomiting; the vomited matters are generally green in color; as a rule, colic and diarrhœa also occur. These symptoms follow pretty rapidly upon the introduction of the poison. The secondary action does not set in generally for several hours, in some cases not for four or six hours, and even longer. The secondary symptoms are headache, giddiness, but especially

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[1] Observation d'empoisonnement par les granules de digitaline. Union méd. No. 99. p. 398. 1852.

diminished frequency of the pulse, followed by distress and oppression, and accompanied by more or less dyspnœa, coldness of the features and of the extremities, and cold perspiration. The cardiac pulsations may sink to 40 in the minute. The consciousness is generally undisturbed, but there is, in most cases, a tendency to sleep, and great lassitude; some loss of power of vision is often observed. Lersch[1] tells us of a man suffering from dropsy who twice took an infusion of digitalis containing in each dose a scruple of the foxglove leaves. His sight afterwards began to fail, and he screamed very loudly, while his pulse beat 44 in a minute. Though his sight returned after about eighteen hours, he could not for some time distinguish color: he confounded green with white, etc. In the course of the action of the poison convulsions came on; indeed, they are often present in digitalis-poisoning. Other symptoms are: falling of the temperature, and continued diminution in the frequency of the pulse; finally, sopor and coma set in, with general cyanosis and occasional convulsions, and death ensues from carbonic acid poisoning. Loud tracheal râles, with foaming at the mouth, mark the closing scene. If the case takes a favorable turn, the symptoms gradually give way, the pulse becomes quicker, the respiration more rapid, the features recover their warmth, and then the normal condition is gradually restored; generally the heart-beat remains for some time slower than normal, and sometimes headache, want of appetite, etc., last as long as a week. The action of digitalis on the heart is so marked that, even in the stage of recovery from the effects of the poison, very slight causes suffice to bring on cardiac paralysis. In the case given by Mazel, and quoted above, after the pulse of the poisoned girl had risen (from 42 to 60), and decided improvement had taken place (on the fifth day), she suddenly died of collapse in getting into bed after an action of the bowels.

The whole course of digitalis-poisoning is rather subacute, lasting for many days. As the onset of the symptoms is very gradual, so the action of the poison generally lasts a considerable time. There have been cases in which death did not occur till

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[1] Wirkungen der Digitalis purpurea. Rhein. westphäl. Corr.-Blatt. No. 15. 1845.

the thirteenth day, but sometimes the case ends fatally in five days. So, again, recovery is a very tedious and gradual process, and it is some time before it is actually complete.

Analysis of Symptoms—Character of Digitalis Poisoning.

Digitalis, its preparations, and its active principles, considerably excite the sensory nerves of the mucous membranes with which they come into direct contact, so that they produce violent sneezing, from excitement of the nasal mucous membrane, a bitter and nauseous taste in the mucous membrane of the mouth, and sickness, tendency to vomit, and actual vomiting in the mucous membrane of the stomach.

As soon as the principles of digitalis have reached the blood they exert a considerable action on different organs and organic systems. Its most striking and important action is on the heart and its movements, so that digitalis is essentially a cardiac poison, and causes death by its action on the heart. It is not to be wondered at, then, that the action of digitalis on the heart has been the subject of searching investigation both on the part of ancient and modern physicians. Stannius[1] observed that when he subjected cats to the action of digitalis the cardiac pulsation became slower, as well as irregular and intermittent, and that the diastolic movements finally ceased, and could not be excited again by direct irritation, whence he concluded that there was paralysis of the cardiac muscle and its motor nerves. This paralysis of the heart set in much sooner when the poison was introduced directly into the veins. Thus its chief physiological action is also that which makes it a fatal poison ; a fact which has been confirmed by all succeeding investigators, who have further enriched our knowledge of the mode of action, and the different stages of action, of this poison.

L. Traube[2] has done essential service in this direction by his

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[1] Untersuchungen über die Wirkung der Digitalis und des Digitalins. Arch. f. physiolog. Heilkunde. 1851. X. Bd. 2 Heft. p. 177 ff.

[2] Deutsche Klinik. No. 8. 1851. Annalen d. Charité-Krankenhauses. II. Jahrg. p. 19 ff. 1852, oder gesammelte Beiträge. I. Bd. p. 190 ff. 252–276, und Berl. klinische Wochenschrift. 1870. Nos. 17 u. 18. ; 1871. Nos. 31 u. 33.

experiments on dogs, and he has drawn a great number of kymographic curves. The following are Traube's results as to the action of digitalis:

1. Small quantities of digitalis, or larger ones in the first stage of their action, cause retardation of cardiac contractions and increase of blood-pressure.

2. Larger quantities retard the pulse and diminish blood-pressure.

3. Very large quantities of digitalis accelerate the cardiac contractions and diminish blood-pressure still more, or this remains at a low point.

If this third stage ends in death the observation of Stannius is confirmed, that there is gradual diminution and irregularity of cardiac contractions, with great decrease of blood-pressure, and eventually cessation of diastolic movement.

Traube gave his attention to the consideration of the question, what causes the initial retardation and secondary acceleration of cardiac movement, and the result of his researches led him to this conclusion: That the vagus is at the outset excited by digitalis at its central origin as well as at its terminal extremities in the heart; that therefore small and moderate doses diminish cardiac pulsation, but large doses of the poison produce paralysis of the same parts of the vagus, and this paralysis accounts for the increased frequency of cardiac pulsation in the third stage of the action of digitalis. When Traube administered very large doses of digitalis he could not succeed in retarding the accelerated action of the heart by irritating the vagus—a proof that in that stage of the action of digitalis the extremities of the vagus are insensible.

The nerves which have the effect of accelerating cardiac movement are not, it would appear, specially influenced by digitalis.

On the other hand, the cardiac muscle (and perhaps the motor ganglia in it) is acted upon considerably by digitalis.

The heart itself becomes certainly excited or more excitable by small doses of digitalis, as Eulenberg[1] observed; this investigator discovered that direct application of digitalin accelerated

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[1] Allgemeine med. Centralzeitung. No. 98. 1859.

cardiac pulsation in the heart of frogs, acceleration alternating with intermission. The same irritation of the heart was observed by Dybkowsky and Pelikan;[1] indeed, in their experiments this irritation was often so strong that the heart remained for some time in systolic contraction. Boehm[2] also observed the same thing; in his experiments several muscular bundles remained continuously contracted even during the diastole, so that the latter was incomplete and afterwards the whole ventricle remained contracted, and the auricles had not power to force the blood into the ventricle. Boehm observed (as did Dybkowsky and Pelikan) this arrest of the heart in systole to set in at a time when the inhibitory influence of the vagus by digitalis was still rising, so that he could succeed in overcoming the persistent systolic contraction by slight electric shocks. The same cardiac excitement was also observed in the experiments of Blasius,[3] who noticed in an artificial circulation the increase of the quantity of blood forced out of the heart in a given time, accompanied with an acceleration of cardiac pulsation.

This stimulation of the cardiac muscle has the effect, especially when accompanied with excited action of the vagus, of retarding the cardiac pulsation. If once the systolic contraction, as Boehm observed, is slackened, certain systolic beats become incomplete or fail altogether, and so retardation of the heart-stroke takes place. This excitement, or, as this condition may perhaps be considered, this increase of the excitability of the cardiac muscle gradually disappears, and when small doses are concerned gives place to the normal condition, *i. e.*, the cardiac pulsation gradually returns to its original rate; when large doses of digitalis have been given the heart acquires a condition of diminished excitability or paralysis. According to Traube's researches the vagi are paralyzed by large doses of the poison, earlier than the cardiac muscle, otherwise there could not be so remarkable an acceleration of the cardiac pulsation before death.

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[1] Zeitschrift für wissenchaftliche Zoologie. XI. 279.

[2] Pflueger's Archiv für die gesammte Physiologie. V. 153. und Dorpater med. Zeitschrift. IV. 63.

[3] Verhandlungen der physical. med. Gesellschaft. Würzburg. N. F. II. 49.

When paralysis of the heart itself sets in, the pulsations become slower and weaker, and at last cease altogether.

The variations in the blood-pressure under the influence of digitalis, as they are represented in Traube's theses, are the result of several factors. In the first place, it is clear that, while the action of the heart under the influence of digitalis is increased, since the vis a tergo compared with the quantity of blood to be set in motion is considerable, and the quantity of blood to be propelled in a given time is large, there must be increase of blood-pressure. Further, it is self-evident that in the stage of cardiac paralysis precisely the opposite condition must be set up. But another important agency comes into play to increase these effects, and that is, the influence of digitalis on the vessels. Brunton[1] had already suggested that digitalis caused contraction and afterwards relaxation of the peripheral vessels. Meyer[2] came to the same conclusion, but it was reserved for Ackermann[3] to exhibit such contraction and distention by direct observation in the mesenteric vessels of the rabbit.

Traube then attempted to prove that this contraction and subsequent dilatation of the vessels arose from a primary excitement and secondary paralysis of the vaso-motor centre, and he supported this theory by an experiment which showed that, after section of the spinal marrow, digitalis did not increase the blood-pressure. Ackermann, on the other hand, observed increase of blood-pressure during this experiment; therefore he, with Brunton and Meyer (which last also observed contraction of the vessels by digitalis even after the section of the vaso-motor nerves), concludes that digitalis acts directly upon the peripheral extremities of the vaso-motor nerves. The main influence of digitalis upon the blood-pressure is, however, clearly the result of its influence on the heart, as appears from the researches of Boehm.[4]

This investigator succeeded in producing increase of blood-pressure by digitalin, when he, by tying the aorta beneath the

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[1] On Digitalis, with some Observations on the Urine. London. 1868.

[2] Untersuchungen aus dem physiolog. Laboratorium in Zürich. Wien. 1869. p. 71 ff.

[3] Deutsches Archiv für klinische Medicin. XI. p. 125 ff.

[4] *Pflueger's* Archiv. V. S. 153 ff.

diaphragm, almost completely excluded the condition of the small vessels from any influence on the blood-pressure.

Although we believe that this account of the mode in which digitalis affects the cardiac contraction and the blood-pressure expresses the present state of our knowledge, a few words must be devoted to the views which different investigators have advanced as to the influence which the action of the poison on the vagus has on these alterations in blood-pressure, and the converse.

Traube had originally regarded the change in the blood-pressure as dependent on the action of the poison on the vagus. Winogradoff,[1] however, showed that the retardation of the pulse produced by irritation of the vagus was not followed and accompanied by increase of blood-pressure, as Traube thought, but by a decrease. Therefore, increase of blood-pressure cannot depend on the irritation of the vagus by digitalis. After Bernstein had shown that every increase of blood-pressure produced an exciting effect on the root of the vagus, and therefore retarded cardiac pulsation, the conclusion was inevitable that in the action of digitalis the primary result is increase of blood-pressure; then, secondarily, dependent on this increase, follows irritation of the vagus, and consequently retardation of the pulse. But however plausible this view may be, yet the influence of the poison is by no means limited to the central origin of the vagus, but extends also to its cardiac extremities, as Traube's experiment evidently proves, when, after large doses of digitalis, he tried in vain to diminish the cardiac pulsations by irritation of the vagus. But another experiment of Traube's shows that the vagus is excited throughout its whole extent, and, therefore, that digitalis acts on its root independently of increased blood-pressure. When, by section of an animal's spinal marrow, he had excluded a not unimportant factor in the increase of blood-pressure, viz., contraction of the vessels, and then administered digitalis, he observed a retardation of cardiac pulsation in spite of the abnormally low pressure of the blood; nay more, he observed that the retarding

[1] Ueber die Einwirkung des Digitalins auf den Stoffwechsel und dem mittleren Blutdruck der Arterien. Virch. Arch. XXII. 5. 6. p. 457. 1861; und Petersburger med. Zeitschrift. 1. 4. p. 116. 1861.

action on the pulse was stronger than in an uninjured animal. Therefore we must admit a direct primary action of digitalis on the vagus.

We gather, then, from what has been said, that in frogs poisoned by digitalis, cessation of cardiac movement is twice observed during the action of the poison: at the outset a systolic, and at the close a diastolic cessation. In case of poisoning in the human subject, so far as my knowledge extends, the latter only is observable. All other conditions, as to retardation and acceleration of cardiac pulsation, and increase and diminution of blood-pressure, are to be observed equally in the human subject and in the dog. The rapidity with which the different stages succeed one another depends chiefly on the quantity of poison taken into the body, and the rate of its absorption.

The decrease of temperature is the result of the change in the capacity of the peripheral vessels, which are acted on by the digitalis, and it naturally results from an increase in the outflow of heat. The vomiting, which is so frequent a symptom in every form of administration of digitalis, is most probably to be attributed to the action of the poison on the nervous centres. According to O. Nasse,[1] the peristaltic contraction of the intestine is quickened by the digitalis, which would account for the diarrhœa which is often present. The voluntary muscles are also affected by digitalis. Buchheim and Eisenmenger[2] show that digitalis, whether applied directly or acting systemically, ultimately altogether destroys the excitability of the muscles. This explains the lassitude and rigidity which attend many cases of poisoning. The influence of digitalis on the brain is inconsiderable, even if all the cerebral phenomena which appear in cases of poisoning may not be traced to disturbances of circulation. Neither has it any great action on the spinal marrow; yet Weil[3] and Meihuizen[4] observed in the frog a diminution of reflex action, resulting from excitement of Setschenow's reflex inhibitory centre. The

[1] Beiträge zur Physiologie der Darmbewegungen. Leipzig. 1866. p. 63.
[2] Eckhard's Beiträge zur Anatomie u. Physiologie. V. p. 37.
[3] Arch. f. Anat. u. Physiolog. 1871. p. 252 ff.
[4] Arch. f. d. gesammte Physiologie. VII. p. 201.

convulsions which come on in the last stage of cases of poisoning which end fatally are to be regarded as the result of carbonic acid poisoning, following upon paralysis of the heart. It was thought for a long time that digitalis exerted some influence on tissue-changes; thus G. Siegmund[1] states that digitalis has the effect of increasing the flow of urine, while it diminishes the amount of urea secreted by eight grains a day, although more nourishment has been absorbed. Mégevand[2] also found that the secretion of urea decreased under the influence of digitalis; Winogradoff[3] also found that not only urea, but the chlorides, phosphoric acid, and sulphuric acid were diminished. Yet all these statements are by no means conclusive as to a diminution of tissue-change as regards the secretion of products of the decomposition of albumen, as the experiments on changes of tissue were not carried out with the precautions which are so necessary. We cannot, however, be surprised at the results arrived at, when we take into consideration the influence of digitalis on the stomach, intestine, and digestion generally. A series of experiments which I myself performed, but without publishing them, leads me to conclude that no alteration worth mentioning takes place in the decomposition of albumen under the influence of digitalis. In doses which augment the blood-pressure, and thereby increase the secretion of fluids, somewhat more urea is found in the excretions; where the blood-pressure is decreased, on the other hand, there is somewhat less in proportion to the ingesta.

The same remarks apply to the decomposition of carbonaceous matters contained in the body and in the ingesta.[4]

Digitalis, in doses which increase the blood-pressure and the cardiac pulsations, promotes the secretion of carbonic acid and the assimilation of oxygen; it diminishes these factors when large doses are given, which reduce the action of the heart and diminish the blood-pressure.

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[1] Einwirkung des Digitalins auf die Durchschneidung des Nervus Vagus und auf die Harnstoffausscheidung. Virch. Arch. Bd. VII. p. 238. 1854.

[2] Gaz. hebdomad. de méd. 1870. No. 32.

[3] Virch. Arch. XXII. 5. 6. p. 457. 1861.

[4] See *v. Boeck* und *Bauer*, Zeitschr. f. Biologie. 1874. p. 367 ff.

Results of Autopsies.

Autopsies of cases of digitalis-poisoning are very rare, and in the few which have been carried out thoroughly, no characteristic changes have been found of digitalis exclusively. When the poison has been introduced through the mouth, we usually find detached patches of inflammation on the serous covering of the stomach—some mucus in the mouth and in the alimentary canal. In a few cases engorgement of the brain is present, in others it is absent. In other respects we find just those appearances which are the constant result of cardiac paralysis. The heart is flaccid and full of partially coagulated blood ; there is venous hyperæmia, sometimes œdema of the lungs ; vascular engorgement of the liver, spleen, kidneys, etc. In some cases we find portions of digitalis powder or leaves, etc., in the contents of the stomach.

Diagnosis and Differential Diagnosis.

The diagnosis of digitalis-poisoning rests on the following symptoms: vomiting, rarely absent, generally very persistent, progressive retardation with intermission of the pulse, gradual loss of cardiac power, and diminution of blood-pressure, while consciousness remains comparatively undisturbed. Valuable aid is afforded to the diagnosis by the history of the case, *e. g.*, if digitalis had been prescribed, etc. Digitalis-poisoning, as distinguished from other cardiac poisons, may easily be confounded with heart-disease ; the weak and intermitting pulse may give rise to this mistake. The remarkable muscular debility which attends digitalis-poisoning may assist in the diagnosis.

Prognosis.

Although digitalis and its products are among the most powerful of cardiac poisons, they rarely prove fatal. The prognosis is favorable if vomiting comes on at an early stage, so that less of the poison is absorbed ; it is also a favorable symptom if the

reduction of the number of pulsations and of cardiac action is inconsiderable, and *vice versa*. It is an evil omen when the pulse sinks below 40 ; the same may be said of a violent acceleration of the pulse after preceding retardation. A gradual acceleration of the pulse must be regarded as a favorable sign, and as the first step towards recovery, although even in this case there is still the danger of sudden collapse. The prognosis is therefore doubtful till the normal pulsation has returned, as digitalis is decidedly cumulative in its action, so that its action may persist for a long time, and even increase in severity.

Treatment.

With regard to the treatment of digitalis-poisoning, emetics and the stomach-pump are the most important remedies ; but as emetics are generally effectual in eliminating this poison, the use of the stomach-pump may be avoided. Tannin is to be recommended as a so-called chemical antidote, as it forms a chemical compound with the active constituents of digitalis; this compound, however, is by no means insoluble,[1] and emetics must be given all the same. If the poison has once begun to act, remedies must be employed, which are calculated to promote cardiac action and avert cardiac paralysis. Among these are camphor, ether, alcohol, wine, coffee, irritants of the skin, mustard poultices, etc. There are no physiological antidotes to digitalis in the actual sense of a real antagonism. The oil of elemi, which was recommended by Mannkopf[2] as an antidote in digitalis-poisoning, because it paralyzes the vagus, has, however, no claim to be regarded as such, because digitalis itself in large doses paralyzes the vagus, and also because (as we learn from later works on the action of digitalis) its influence on the vagus is insignificant in comparison with its effects on the heart itself, especially when the poison has been taken in large doses. Delphinine, which, according to Boehm's researches, counteracts the effect of digi-

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[1] *Gustave Aimé Becker*, Études botaniques, chimiq. et toxicolog. sur la digitalis pourprée. Strassburg 1864.

[2] De olei Elemi ætherei natura. Berlin. 1858; and also Virch. Arch. XV. p. 192. 1859.

talis in arresting cardiac action, is itself so violent a poison, that its action may be as dangerous as digitalis itself; up to this time no practical trial has been made of it.

Changes which Digitalis and its Products Undergo in the Organism.

The active constituents of digitalis are absorbed by the mucous membrane of the stomach and small intestine, and even by that of the large intestine. This process is, however, in general very slow; *e. g.*, A. Brandt,[1] who made numerous experiments on animals under the superintendence of Dragendorff, after four and a half hours, found the poison still in the stomach; none of it had passed into the intestine. I have often convinced myself that the constituents of digitalis may be absorbed by the rectum, for I have observed the characteristic effects of digitalis on the heart, after its administration as an enema to patients with heart-disease. Taure[2] calls attention to the possibility of endermic poisoning by digitalis, as he saw it occur through a wound on the skin. Chrzonszewsky also observed violent symptoms of poisoning in a boy who had remained a long time in a bath of infusion of digitalis. Here the poison must have been absorbed through the unbroken cuticle, as he had excluded the mucous membrane of the rectum and of the urethra. Browne[3] also found that when he applied moistened digitalis leaves to the skin of a patient, the pulse became slower and increased diuresis was set up. The detection of the products of digitalis in the blood, in the tissues, and in the urine, is difficult and uncertain; it would, therefore, appear that the active constituents of digitalis suffer decomposition in the organism.

Chemical and Physiological Tests.

The chief test by which the active constituents of digitalis can be recognized, is that of Grandeau,[4] with bromine and sul-

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[1] Experimentelle Studien über die forensische Chemie der Digitalis u. ihrer wirksamen Bestandtheile. Dorpater Diss. 1869.

[2] Archiv. général. 1864, Oct. p. 113.

[3] Med. Times. Jan. 25. p. 85. 1868.

[4] Gaz. des Hôpit. 1864. 69.

phuric acid. The substance to be tested is moistened with concentrated sulphuric acid, then exposed to the vapor of bromine, when it assumes a violet color. Otto[1] dissolves the substance to be tested in concentrated sulphuric acid, and then drops a minim of bromine-water into the solution with a glass rod, and thus obtains the same violet color. Dragendorff[2] moistens the mass to be tested with sulphuric acid, then adds one drop of a mixture containing one part of hydrate of potash and three parts of water, and adds to this so much bromine as will color the whole of a pale yellow; then violet streaks appear, which retain their color for a very long time. If digitalin predominates in the mass, the color approaches to blood-red, if digitaleïn predominates, the streaks incline rather to purple.

With hydrochloric acid the active constituents of digitalis give a very beautiful emerald green color.[3] For the separation of the poison from organic substances, the best mode to follow is Dragendorff's. Pulverize the mass, concentrate it, if necessary, by careful evaporation, and add enough glacial acetic acid that the whole may contain at least 50 per cent. of acid. After it has stood for some time, add water to it so as to dilute the mass to a thin paste, and digest at a temperature of from 104° to 113° Fahr. for about twenty-four hours. Now add three times the quantity of spirits of wine, digest again for twenty-four hours, after which filter the mass. Then carefully separate the filtrate from the alcohol by distillation, filter the residual watery fluid again, and shake it twice with half its volume of benzol at 122° Fahr.; the benzol does not, however, absorb all the constituents of digitalis, but leaves digitaleïn in the mass. Therefore the acid watery fluid must be separated from the benzol and shaken at 95° Fahr., with one-quarter its volume of chloroform, which separates the digitaleïn from the rest of the mass. In the evaporation the glucosides remain behind and can be used for the chemical and physiological tests.

The physiological test depends upon the action of the poison

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[1] Anleitung zur Ausmittelung der Gifte. p. 32. 1867.

[2] *A. Brandt*, Experimentelle Studien, etc. See above.

[3] *Homolle* et *Quevenne*, Mémoire sur la Digitaline. Bull. de l'Academ. de méd. XV. p. 332.

on the frog's heart. The hearts of two frogs having been exposed, the substance to be tested is subcutaneously injected into one of the frogs. If the cardiac pulsations slacken, if separate groups of the cardiac muscles contract permanently, if the whole ventricle contracts, the heart at the same time assuming a bright-red color, and if, finally, the ventricle remains in a state of systolic contraction, while the auricles are distended, we are justified in concluding that we have administered a cardiac poison, which is probably digitalin. But the chemical test is safer and more reliable than the physiological one, and the latter is only to be regarded as a complement to the former. When the physiological test is applied by introducing directly into the frog the contents of the stomach, or the matters vomited, it is still more unsatisfactory, because the substances are generally too diluted ; so also the administration of an alcoholic extract of the contents of the stomachs of dead bodies is of little value, since such extracts may act upon frogs as cardiac poisons without the presence in them of any poisons introduced from without.[1] In the case of de la Pommerais, the chemical test for digitalin failed. Tardieu and Roussin tried to isolate the poison by dialysis; they thus obtained a substance with which they killed dogs and other animals, with the symptom of gradual cessation of cardiac pulsation.

Poisoning with Veratrine.

Veratrine, $\text{Θ}_{32}H_{52}N_2\text{Θ}_8$ (G. Merck), was discovered in 1818 by Meissner in the seeds of sabadilla, and in 1819 by Pelletier and Caventou also in the white hellebore; it is to be found in all species of veratrum (colchiaceæ and melanthaceæ). The most important plants of this tribe are, first, Veratrum album, which grows in Southern Europe, and contains the alkaloid chiefly in its roots; secondly, Veratrum officinale, which is indigenous to the Antilles, and the poison of which lies chiefly in the seeds

[1] Comp. *E.* and *G. Homolle*, L'Union médic. p. 295. 1872.

which are known and used in medicine under the name of cevadilla seeds (semina sabadillæ); thirdly, Veratrum viride,[1] a native of America, whose root has only recently been introduced into the pharmacopœia. In the cevadilla seeds, besides veratrine, a second alkaloid is present, sabadilline, and a third, sabatrine; the root of the Veratrum album also contains, in addition to veratrine, another alkaloid to which the name of jervine has been given.

Veratrine is a white powder which, when examined under the microscope, is found to be crystalline. G. Merck obtained it in long, colorless, transparent, rhomboidal prisms, which were decomposed in atmospheric air, and thus rendered porcelain-like and friable. It is free from odor, but irritates the nasal mucous membrane so as to provoke the most violent sneezing; it has a sharp and burning taste and an alkaline reaction. It is very sparingly soluble in cold water, and but slightly so in boiling water (1:1000), but it is readily soluble in alcohol, less so in ether (1:10); it is pretty freely soluble in chloroform, amylic alcohol, and benzol. Veratrine is very readily soluble in acids, in combination with which it forms salts which generally present a gum-like appearance.

Etiology.

Poisoning by veratrine occurs when a sufficient quantity of poison, whether pure or in the form of the above-named plants, is introduced into the system. It usually arises from mistaking veratrine for other substances, such as ground pepper, caraway seeds, etc. Poisoning by medicinal preparations is not infrequent. Blas[2] reports a case of two children, one and one-half and three and one-half years of age, who were dangerously poisoned by drinking a liquid containing veratrine, which had been prepared for destroying lice in cows. Buckingham[3] communicates a case in which the lives of two men were endangered by using

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[1] Many recent investigations have shown that the alkaloid or alkaloids of veratrum viride are not identical with veratrine. Consult U. S. Dispensatory, Fourteenth Edition.—E. C.

[2] Verhandlungen der naturforschenden Gesellschaft in Freiburg. II. 2. p. 173. 1860.

[3] Americ. Journ. of Med. Science. p. 563. Oct. 1865.

the tincture of American hellebore instead of tincture of valerian. Nivet and Giraud[1] report a murder committed by a woman upon her mother and two brothers through the medium of veratrine and powdered white hellebore. E. Peugnet[2] mentions the case of a nervous woman who was very violently poisoned by a homœopathic mother-tincture of white hellebore. The amount of veratrine contained in this mother-tincture is stated at seven-eighths of a grain. Another case is given by Paget-Blacke,[3] in which poisoning occurred from taking a liniment internally, which contained two and one-quarter grains of veratrine, instead of a draught. It is difficult to say what amount of veratrine is sufficient to poison. The largest dose permitted by the German Pharmacopœia is one-thirteenth of a grain (0.005) of veratrine per dose, and a little less than half a grain (0.03) per day; of white hellebore root four and a half grains (0.3) per dose, and eighteen grains (1.2) per day. Cats are killed in from one to two hours by three-quarters of a grain of veratrine.

Symptoms and Course of Veratrine-Poisoning.

As far as I know, in all cases of veratrine-poisoning the poison is received through the mouth. In general, shortly after it has been taken, a burning sensation is felt in the throat and gullet; the secretion of saliva is increased; sometimes there is inability to swallow; the painful burning sensation extends to the stomach and the alimentary canal. Violent retching and vomiting then set in, and a considerable quantity of the poison is often thus eliminated. Severe diarrhœa, with pain in the bowels, and tenesmus are the next symptoms. Apart from these gastro-enteritic symptoms, others are developed, affecting more distant organs. Some of the most prominent are violent headache and palpitation of the heart, anxiety; the skin becomes covered with perspiration; we may also have giddiness, or fainting-fits; the pulse becomes slower and more feeble, the respiration slower, superficial, and labored. Consciousness remains intact. The

[1] Gaz. hebdomad. VIII. p. 31. 1861.

[2] Med. Rec. May 1. p. 421. 1872.

[3] St. George's Hospital Rep. V. p. 69. 1871.

pupils are generally dilated (more rarely contracted), the eye-balls fixed and motionless, or else rolling. Involuntary muscular twitchings appear in the form of facial contortions and subsultus tendinum. Sometimes, but very rarely, convulsions set in; in animals, however, they are constant. In many instances a feeling of formication and violent irritation of the skin have been observed.

If the case takes a favorable turn, the first step towards recovery is the gradual cessation of vomiting and diarrhœa; then the pulse becomes stronger and fuller, the respiration more natural and less labored, and the muscular twitchings cease, but the insensibility of the skin may continue for some time. If, however, the symptoms which we have enumerated should become aggravated, a fatal result may be expected, probably aided by the loss of fluid from the vomiting and diarrhœa. Death is to be regarded as the result of the action of the poison on the heart. But paralysis of the respiratory organs must be taken into consideration as well as that of the heart. In cases which terminate fatally respiration always becomes more slow and labored, so that cyanosis sets in as a consequence of defective respiration and cardiac contraction. The whole course of the poisoning process is somewhat acute. One of the children mentioned by Blas recovered three-quarters of an hour after the first symptoms of poisoning appeared. The woman mentioned above recovered on the second day. When death occurs, it is also tolerably rapid, *i. e.*, in about twenty-four hours. In the case of the three murdered persons reported above, death did not, however, ensue for a long time, but it is probable that the dose of poison was not administered all at once, but in small quantities, frequently repeated.

The poisoning had begun towards the end of June; there were remissions in the attacks of illness of the two brothers—aged respectively 21 and 22—with recurrences, and so the thing went on till towards the end of August, when they were found by a physician in a state of great debility and emaciation, with anxious countenance and dark circles round the eyes; they were delirious and restless, with aberration of intellect; they were also suffering from gastric and intestinal catarrh and dysentery.

The elder died on the 31st of August, the younger on the 14th of September; that is to say, nine and eleven weeks respectively after the first administration of the poison. The mother of the murderess was taken ill with the same symptoms on the 25th of August, and did not recover till the 20th or 22d of September. In her case also the protracted course may have been the result of frequently repeated doses of veratrine.

As sequelæ, in the case reported by Paget Blacke, violent cutaneous irritation, and a convulsive closing of the jaws, which often came on during talking and laughing, continued for a long time.

Analysis of Symptoms—Mode of Action of the Poison.

The action of veratrine upon the alimentary mucous membrane is the point of chief interest. Veratrine acts as a powerful irritant on the sensory nerves of the mucous membrane of the nose, mouth, stomach, and intestine. Hence violent sneezing, burning in the throat, with a reflex flow of saliva, pain in the stomach, with reflex vomiting and diarrhœa. But this action is unattended with ulceration or inflammation. Veratrine also causes much heat and redness of the cuticle when applied externally or as an ointment.

The influence of veratrine upon the motor apparatus, especially the muscles, is, however, still more important than its local action. The muscles are affected in a peculiar manner by veratrine. Leonidas van Praag [1] states that the tension of the muscles is destroyed by veratrine. Koelliker [2] infers from his experiments that the muscles become paralyzed and soon rigid under the influence of veratrine, and this is confirmed by Guttmann.[3] The investigations of v. Bezold and Hirt [4] show

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[1] Toxicologisch-pharmacologische Studien über Veratrin. Virchow's Archiv. Bd. VII. 2. pp. 252–298.

[2] Physiologische Untersuchungen über die Wirkung einiger Gifte. Virch. Archiv. Bd. X. p. 235 ff.

[3] Arch. f. Anat. u. Physiolog. p. 495. 1866.

[4] Arch. f. patholog. Anatom. X. p. 257. und Untersuchungen aus dem physiologischen Laboratorium zu Würzburg. 1 Heft. 1867.

that veratrine at first increases and afterwards diminishes muscular excitability. A muscle poisoned by veratrine reacts for a long time to direct or indirect irritation by a twitching, which at the first glance might be mistaken for tetanus, but which is quite different in its course, and can be excited by very few poisons except veratrine.[1] The contraction is performed in the ordinary time, but the relaxation is very much protracted, the descending stroke of the myographion curve presenting a different appearance, as Fick and Boehm[2] and others have proved, so that the descent, instead of being uniform, is broken; as, *e. g.*, at first rapid relaxation up to a certain point, then retardation of the fall, or initial relaxation succeeded by contraction, so that such a myogram bears some resemblance to the curve of the dicrotic pulse; or the muscle may remain for some time at the highest point of contraction and then relax with more or less rapidity. This clearly proves that the contraction caused by veratrine is no tetanus, and this is further confirmed by the fact that no secondary tetanus extends from the veratrine-contracted muscle to a nerve lying close to it, which must occur if the muscle were affected by real tetanus (Fick and Boehm). Fick and Boehm are of opinion that this tardy relaxation is due to an influence exercised by veratrine upon those substances which are generated when the muscle is excited, which stimulate contraction by their presence, and produce relaxation by their disappearance. The formation of these substances is, according to these authors, promoted by veratrine, so that they require a longer time for their disappearance, upon which the relaxation of the muscle depends. They are led to this conclusion from the heat-producing effect, during contraction, of the muscle influenced by veratrine, as compared with that of the healthy muscle. The veratrinized muscle generates much more heat upon simple irritation than the healthy muscle; the former makes much more considerable effect upon Heidenhain's apparatus than the healthy muscle under simple irritation. Hence the

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[1] *Weyland*, Vergleichende Untersuchungen über Veratrin, etc. Giessen. 1869. *Buchheim* u. *Eisenmenger*, Eckhardt's Beiträge zur Anat. u. Physiolog. V. p. 37.

[2] Ueber die Wirkung des Veratrins auf die Muskelfasern. Verhandlungen der phys. med. Gesellsch. in Würzburg. N. F. III. p. 198. 1872.

processes of combustion in the veratrinized muscle are stimulated by the poison. The other possible hypothesis, that veratrine hinders and limits the disappearance of the substances determining the contraction of the muscles, which are formed only in normal quantity, is thus proved to be untenable.

Authors are at variance as to the question whether the motor nerves are sympathetically affected by veratrine. Whereas Koelliker entirely sets aside the participation of the nerves, van Praag, and more lately v. Bezold and Hirt, have maintained that there is an initial increase and subsequent diminution of their excitability. Again, Fick and Boehm, in their lately published work, insist upon excluding the nerves. For they found the negative current-oscillation in the nerve, in the stage of so-called veratrine paralysis, just as in the normal nerve; they also found that curare exerts no influence on the veratrine-poisoned muscle and nerve, and on many essential points they question the experiments of v. Bezold and Hirt. It is a fact that when a veratrinized muscle is repeatedly irritated, the peculiar veratrine retardation in the relaxation of the muscles soon disappears, and we get the same myograms as in the normal muscle. v. Bezold and Hirt assert that they have observed this disappearance of the veratrine condition in the muscle even when it has been stimulated through its nerve. When they, then, applied the electrodes to another nerve-tract, the veratrine condition returned, to give way again to the normal condition after a few shocks. Fick and Boehm observed this circumstance to occur from one and the same nerve-tract, if they interposed a pause between the shocks. They therefore conclude that the pause of rest is the main point, and not the change in the nerve-tract excited.

Even though these investigations of Fick and Boehm cannot be accepted as completely setting aside the statements of v. Bezold and Hirt—that the increase and diminution of excitability appear sooner in the nerves than in the muscles, and earlier under indirect than under direct irritation — and, therefore, a sympathy of the nerves is not completely disproved, yet so much is clear, that the action of veratrine mainly affects the muscles, and that its influence on the motor nerves is comparatively subordinate. This influence of veratrine on the muscles explains,

at least partially, the phenomenon of muscular contractions, as they accompany veratrine-poisoning. Another cause of these convulsions lies in the action of the poison on the motor nerve-centre. That convulsions proceed from the centre is proved first by the fact that in animals all the muscles are equally affected, and secondly by the experiment which proves that the muscles are thrown into convulsions even when the arteries leading to them have been ligatured before the administration of the poison, so that they cannot themselves have been brought into direct contact with the poison.

As to the action of veratrine upon respiration, v. Bezold and Hirt state, as the result of their investigations, that in the early stage of the action of the poison there is an irritation of the terminations of the vagus in the lung; thus respiration is accelerated by injecting veratrine into the central end of a vein; soon, however, respiration becomes slower, and finally ceases altogether; this would appear to indicate an influence on the respiratory centre, amounting to paralysis.

Toxicology is, however, chiefly concerned in the action of veratrine on the heart and circulation, as the most decisive symptoms of the poisoning depend on their disturbance. The influence of veratrine on the heart is, however, very complicated. In the first place, the cardiac muscle suffers the same changes as the other muscles, and this would suffice in itself to account for most of the symptoms. The heart, excised and separated from all extrinsic nervous influence, when acted upon by veratrine, at first contracts more frequently and powerfully; later on, the contractions diminish in both frequency and force, till they cease altogether, and cannot be renewed by direct irritation. It is highly probable that the intrinsic cardiac motor nerve-centres take the same share in this process as the muscles. But the regulatory cardiac nerves are also affected by the poison. The vagus is excited at its origin by small doses of the poison; thus in the frog and the rabbit a retardation of pulsation has been observed, which, after section of the vagus, gives place to an acceleration. But the cardiac extremities also of the vagus are at first excited, and afterwards paralyzed. The ultimate result of the action of veratrine on the heart is, therefore, complete paralysis. In the

early stage of the action of veratrine an increase of blood-pressure is often observed, together with acceleration of cardiac pulsation, but later on there is a constant decrease of the blood-pressure. This is attributable not only to the change in the heart, but to the condition of the vessels, for, according to the researches of v. Bezold and Hirt, these are first stimulated and contracted through their vaso-motor centre by the poison, and later on they are paralyzed and dilated. The best way of confirming this fact is to inject the poison into the peripheral extremity of the carotid.

These circumstances account for the whole series of symptoms of collapse which are observed in veratrine-poisoning.

Diagnosis and Differential Diagnosis.

The recognition of veratrine-poisoning as such depends chiefly on the presence of gastro-intestinal symptoms, together with a steady decrease of cardiac action, as well as on the muscular twitchings when they are present. But as these symptoms also attend other poisons, the nature of the diagnosis will necessarily be influenced by the matter vomited, the history of the case, etc. The strongest analogy exists between veratrine- and digitalis-poisoning. But here there are important distinctions as regards time, which may prevent our confusing them with one another. The gastric symptoms and the diminution of cardiac power set in much earlier in cases of poisoning by veratrine than in those by digitalis. The dilatation of the pupils which sometimes attends veratrine-poisoning might lead to its being mistaken for atropine- or hyoscyamine-poisoning; in this case the increased flow of saliva present in veratrine-poisoning, but entirely absent in atropine-poisoning, will enable us to distinguish between them; much dryness and redness of the mucous membrane of the mouth being one of the most characteristic symptoms of poisoning by atropine.

Results of Autopsies.

The few reports which we possess of autopsies performed on

persons who have died from veratrine-poisoning present few characteristic signs of this poison. In contrast to the clinical symptoms we find no traces whatever of inflammation in the stomach and intestine. Generally there are the evidences of death from asphyxia, hyperæmia, and œdema of the lungs, etc., with ecchymosed and hemorrhagic patches, dark fluid blood in the heart, etc.

Prognosis.

The prognosis in cases of veratrine-poisoning depends mainly on the quantity of poison conveyed into the system and absorbed by it. But as vomiting comes on at a very early stage in the action of this poison, a considerable quantity of it is eliminated, and therefore fails to have any effect. Practically the condition of the heart will be the safest guide to a correct prognosis.

Treatment.

The treatment of veratrine-poisoning is simple and self-evident. Emetics ought to be administered at the outset, or, should they be rendered unnecessary by the action of the poison itself, tannin, or remedies containing tannin, should be employed to neutralize the alkaloid. The violent hypercatharsis, if it threatens to become dangerous, must be controlled by opium. To maintain the action of the heart must be the chief point in the treatment. Ether, camphor, and other stimulants may perhaps be sufficient to counteract effectually the effect of veratrine. It is needless to say that particular symptoms may demand other remedies, such as cold compresses for the irritation of the skin, artificial respiration, etc.

Changes which Veratrine undergoes in the System.

Veratrine is absorbed by the stomach; this absorption is not a rapid process, for Dragendorff and his pupils succeeded in finding veratrine in matters vomited by cats, although the vomiting had not begun till some hours after the poison had

been administered. The absorbed veratrine is rapidly secreted in an unaltered condition with the urine, in which it may be detected soon after its administration. Veratrine, however, remains long enough in the blood and the organs to allow of its being detected in that fluid as well as in the heart and lungs. We generally fail, however, to discover it in the liver, gall-bladder, and kidneys.

Chemical Tests.

We are chiefly indebted to Dragendorff[1] and Masing[2] for the chemical tests of veratrine.

The most important points to be inquired into in a case of suspected veratrine-poisoning are the nature of the vomited matter, the state of the stomach and its contents, the upper part of the small intestine, the urine and the blood. The lower part of the small intestine, according to these investigators, contained no veratrine.

Veratrine may be separated from organic substances by preparing an acid watery extract (sulphuric acid and water) and cleansing this by shaking it with petroleum ether, and then, after adding ammonia to the watery extract, the alkaloid is removed by petroleum ether or benzine. Petroleum ether yields a purer product, but benzine extracts it in larger quantity. So we generally use benzine first, and then treat the residuum of this extract first with dilute sulphuric acid and then with petroleum ether. The products thus obtained are proved to be veratrine by the following principal reactions:

It is colored red with cold concentrated sulphuric acid; this red color is also developed when nitric acid is added to sulphuric acid.

According to Masing, the muriatic acid test for veratrine is more sensitive and quite as characteristic. If one-four-hundredth of a grain of veratrine is heated for about two minutes

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[1] Beiträge, etc. p. 85 ff.

[2] Beiträge für den gerichtl. chem. Nachweis des Strychnins u. Veratrins in thierischen Flüssigkeiten u. Geweben. Dorpat. 1868. u. Pharmaz. Zeitschrift für Russland. Jahrg. 7. p. 657.

in a cubic centimetre of smoking muriatic acid, it assumes a beautiful red color (Trapp's muriatic acid reaction).

We can also employ physiological tests for veratrine. The human nasal mucous membrane is irritated by it, so that it sets up violent sneezing; then there is the experiment on the frog. If one-one-hundred and sixtieth of a grain of veratrine, dissolved in a cubic centimetre of water acidulated with acetic acid, be subcutaneously injected into a frog, symptoms of vomiting very quickly come on, the cardiac contractions are retarded, become irregular, and cease entirely after about one and a half hour. If large doses are administered, tetanic convulsions are superadded to the symptoms already mentioned.

APPENDIX.

Veratrum album, as Wood[1] has shown, contains, beside veratrine, two alkaloids: first, *viridine*, soluble in ether, producing muscular debility, trembling, twitchings, clonic convulsions, and death by paralysis of the respiratory muscles. It also increases the secretion of saliva and diminishes sensibility, but consciousness remains intact; it does not cause vomiting.

Secondly, *veratroidine*, insoluble in ether, and acting like veratrine, but weaker.

Therefore, these two alkaloids will not interfere with the veratrine action in veratrum, but rather aid it.

Jervine, which is found in the same plant, has not yet, as far as my knowledge goes, been made the subject of toxicological research.

Sabadine, according to Weigelin,[2] produces at first a slight acceleration of cardiac pulsation, but no other disturbance.

Sabadilline, however, acts like veratrine. These two alkaloids, present in cevadilla seeds, do not disturb, but rather favor the action of veratrine.

These two alkaloids answer to almost the same chemical

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[1] Americ. Med Journ. Jan. 1870.

[2] Untersuchungen über die Alkaloide des Sabadillensamen Dorpat. 1870.

reactions as veratrine. The differences are given in detail in the work of Weigelin which we have mentioned.

Poisoning with Colchicine.

Colchicine, $C_{17}H_{19}NO_5$, is a yellowish-white viscid substance, with a slight aromatic odor and a very strong and persistently bitter taste. It is soluble in water slowly, but, under all circumstances, readily so in alcohol, but not in ether. The alkaloid is found in all parts of the meadow-saffron (Colchicum autumnale), but most abundantly in the seeds and corms.

Etiology.

Poisoning by means of meadow-saffron has frequently occurred, and a number of such cases have been placed on record. Thus McGregor Maclagan[1] gives the history of fifteen cases. And more recently other instances have also been published. Hafner[2] states that a child two and a half years of age ate some seed-capsules of the meadow-saffron, and died in consequence. But cases of medicinal poisoning are more frequent in which the tincture and wine of colchicum seed have been either mistaken for other drugs or taken in over-doses. Thus Jules Roux[3] relates the poisoning of five soldiers under surgical treatment at Toulon, to each of whom two ounces of wine of colchicum seed were given instead of quinine wine, and all of whom died.

Kennard[4] reports a case of a woman, fifty-six years of age, who was violently poisoned by an ounce of wine of colchicum seed, but recovered. Warncke[5] mentions three cases of poisoning by the same tincture. A boy fourteen years of age died of

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[1] On Colchicum Autumnale, etc. Monthly Journ. of Med. Science. January. pp. 1-33 1852.

[2] Fall von Colchicumvergiftung. Würtemberg. med. Corresp.-Blatt. No. 45. 1855.

[3] Empoisonnement et mort de cinq personnes par la teinture de Colchique. Union méd. No. 36. 1855.

[4] Amer. Journ. Jan. 1857.

[5] Hosp. Tijd. 1863. 6.

taking three ounces; a youth of sixteen poisoned himself with between 5 and 6 drachms (20.0–24.0); a youth of seventeen with between 8 and 10 drachms (=32.0–40.0 grammes) of wine of colchicum seed; both recovered. Forest[1] tells of a girl eighteen years of age, who took 18 pills containing nearly twenty-six grains of extract of colchicum, and an equal quantity of extract of colocynth and opium, and died in consequence.

There is also a case of poisoning by pure colchicine, reported by Keller,[2] in which a girl twenty years of age drank a solution of colchicine containing about three-fifths of a grain of colchicine, but afterwards completely recovered.

It is impossible to state accurately what constitutes a fatal dose, but the above data may serve as indications. The new German Pharmacopœia fixes thirty minims (2.0) per dose, and a drachm and a half (6.0) per diem as the maximum, for the tincture as well as the wine of colchicum seed.

Symptoms and Course.

As a rule, the action of this poison runs a protracted course. Two hours, sometimes seven, and even more, may pass without the development of symptoms; though there are cases known, in which the symptoms of poisoning have almost immediately followed the introduction of the poison. These symptoms are, in the first place, an intensely burning sensation in the mouth, violent pains in the bowels, of the nature of colic, accompanied with vomiting and diarrhœa. To these symptoms may be added intense thirst, and violent burning in the throat, œsophagus, and stomach. The vomiting frequently returns after intervals of remission, and is generally preceded by nausea; the diarrhœa is also persistent, and is sometimes hemorrhagic. In the next place, symptoms of disturbed cardiac action, with evidence of acute drain of fluid, set in. In a few cases, the pulse is accelerated or only slightly altered, but far more frequently it is retarded and steadily lowered, and easily compressible. The heart-stroke is usually feeble and retarded, the skin is cool subjectively and

[1] Bull. de la Société méd. de l'Aube. Gaz. des Hôp. No. 36. 1866.

[2] Bericht der Krankenanstalt Rudolfstiftung in Wien. 1867.

objectively, cyanosis spreads over the whole body, but is specially observable in the features. These symptoms are followed by slow and labored breathing; later on, there supervene sensations of utter exhaustion and extreme muscular weakness; and in rare cases ringing in the ears, giddiness, swimming in the head, occasionally slight delirium and convulsive movements. As a rule, consciousness and sensibility remain intact, even up to the last moment. A few cases are recorded of sural cramp and ischuria, as in cholera.

The course of colchicine-poisoning is always comparatively slow. Death seldom supervenes within the first twenty-four hours, but is generally delayed for two and three days, and even longer. In Forest's case the girl died after seventy-four hours, with symptoms of collapse and cardiac paralysis. If the case takes a favorable turn, the pulse rises and the collapse gradually disappears; the skin becomes warmer, cyanosis vanishes, the pulse becomes quicker, fuller, and stronger, the vomiting and diarrhœa cease. Yet even the appearance of these favorable symptoms does not absolutely guarantee a speedy recovery, for, in the first place, collapse is very apt to return in cases of colchicum-poisoning, and secondly, the process of recovery is always slow, and remains for a long time incomplete, whilst diarrhœa and occasional vomiting, accompanied by great muscular weakness, linger on for days and even weeks, and may at length cause death by exhaustion.

Such was the fate of one of the soldiers of Lyons, in the case mentioned above, after he had sensibly recovered from collapse. In Kennard's case recovery did not set in for six days. In that communicated by Warncke, of the youth fourteen years of age, convulsions, accompanied with delirium and violent screaming, did not set in before the seventh day. These last symptoms are, however, very rare, and the convulsions appear to be the result of the onset of carbonic acid poisoning.

Analysis of Symptoms—Nature of the Action of Colchicine.

We may classify the symptoms to which colchicine gives rise as primary and secondary. The primary affect the gastro-intes-

tinal mucous membrane, and comprehend ordinary gastro-enteritis, which is in itself sufficient to account for a number of the symptoms above mentioned, by the acute and considerable drain of fluid ; to this must be added collapse, cyanosis, low temperature, vomiting, diarrhœa, ischuria. The secondary symptoms concern chiefly the heart, muscles, and spinal marrow. Schroff's[1] experiments on animals tend to prove that colchicine is an energetic cardiac poison, which causes death by cardiac paralysis. Nothing more accurate is known as to the action of colchicine on the heart. Hubler[2] traces death exclusively to gastro-enteritis, and regards all the other symptoms as secondary, and dependent primarily on this. Jolyet[3] and Schroff, jun., found an increased reflex excitability in frogs after subcutaneous injection of small quantities of colchicine, while Schroff, jun., upon the introduction of larger doses, observed a heaviness of movements, traceable to paralysis of the spinal marrow. According to Jolyet, colchicine diminishes the power of muscular contraction in frogs, but this is a later symptom than the excitability of the spinal marrow.

It is worth mentioning that vomiting and diarrhœa follow also upon subcutaneous injection. Our information as to the action of colchicine is then extremely scanty, so that further researches are necessary to enlarge our knowledge in this direction. Rossbach hopes shortly to prove that colchicine also exerts a considerable influence on the sensory organs of the body—an effect which would accord with clinical observations.

Diagnosis and Differential Diagnosis.

The recognition of colchicine-poisoning is difficult, since gastro-enteritic symptoms, followed by collapse without loss of consciousness, are common to an entire group of poisons—arsenic, for example, etc. It may be readily mistaken for acute gastro-intestinal catarrh, or confounded with endemic or Asiatic cholera. But there are obvious points of difference upon which to found a diagnosis. In addition to the matter vomited, which may

[1] Oesterreich. Zeitschr. f. pract. Heilkunde. II. 22–24. 1856.

[2] Jenaische Zeitschr. Bd. I. Heft 3. 1864.

[3] Gaz. méd. de Paris. 11. Aug. 1869.

possibly contain portions of the plant, the history of the case, easily obtainable, since there is no loss of consciousness, will be the best means of leading us in the right track.

Prognosis.

The prognosis of colchicine- and colchicum-poisoning, when large quantities of the poison have been absorbed, is, on the whole, unfavorable, for the obvious reason that vomiting does not come on for a long time, and therefore the poison has time to make its way into the absorbents. The most discouraging point in the prognosis is the fact which we have mentioned above, of the probability of recurrence of collapse and cardiac paralysis, after considerable improvement in the symptoms has been observed.

Results of Autopsies.

In autopsies in cases of colchicum-poisoning, we usually find the scalp, the membranes of the brain, and the venous sinus more or less hyperæmic. The blood is usually thick, and of a dark cherry color, and only a very small portion of it is coagulated. The left side of the heart is usually found empty, the right full of blood. Dark-red spots have been found in the œsophagus and stomach, and even small ecchymoses in the latter. The lungs, liver, spleen, and kidneys may or may not be hyperæmic, showing that this hyperæmia is a secondary and not a direct result of the poison. In one case,[1] softening of the spinal marrow was observed, and looked upon as an essential result of colchicum-poisoning. It is, however, highly probable that when the spinal marrow is found in an altered condition, it is only a casual occurrence; at any rate, this single case is not sufficient to prove that the poison acts upon the medulla spinalis.

In another case[2] erosions were found in the bladder, which led to the conclusion that the poison was secreted by the urine. Putrefaction and cadaveric rigidity are not influenced by the poison.

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[1] *Warncke.* Hosp. Tijdsch. 1863. 6.

[2] *Jules Roux,* loc. cit. Un. méd. No. 36. 1855.

Treatment.

In the treatment of persons poisoned by colchicine, the first object to be aimed at is emptying the stomach, if the poison has been introduced through the mouth. If this is accomplished at an early stage, the chances are favorable. Tannin is a so-called chemical antidote, since it unites chemically with colchicine, and forms a somewhat insoluble compound. Tannin precipitates as little as one-three-hundred and fortieth of a grain (one-fifth of a milligramme) of colchicine in solutions of 1 : 2500, according to Dragendorff's[1] statements. The chief symptoms demanding medical treatment are the almost continuous vomiting, and the diarrhœa, which may last several days. For these symptoms opium and ice are the best remedies. If opium, administered internally, cannot be tolerated, it must be administered in the form of an enema, and small portions of ice must be swallowed. It is needless to say that the collapse which the poison produces demands the physican's first care. Cardiac stimulants, such as ether and alcohol in its various forms, camphor, or, finally, subcutaneous injections of acetic ether or camphorated oil, must then be resorted to.

Moreover, the collapse must always be kept in mind when we give opium, as it may be promoted by the narcotic. Even when improvement appears to have set in, the stimulating treatment must be maintained, as experience teaches us that collapse often returns in a later stage of the poisoning. A number of other remedies may be indicated by the symptoms which arise, such as cold douches for stimulation of the skin, etc.

Changes which Colchicine undergoes in the Bodies of Animals.

Colchicine is only partially absorbed in the intestinal canal; and this absorption proceeds very slowly, so that in a given space of time only a very small quantity of the alkaloid is re-

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[1] Beiträge. p. 79 ff.

[2] *Dragendorff's* Beiträge, etc. p. 79 ff.; and Beiträge zu dem gerichtlich-chemischen Nachweis des Colchicins. Dorpat. 1870.

ceived into the circulation. Speyer[2] made numerous experiments on cats with colchicine, under Dragendorff's direction, and found a large quantity of the alkaloid in the fæces and in the contents of the large intestine, whereas none was found in the small intestine, especially its upper part. The poison was almost constantly detected in the urine; it could not, however, be discovered in the blood or the tissues.

In spite of the most careful examination, these investigators never succeeded in recovering the full quantity of the poison introduced, whence they concluded that a part of the colchicine absorbed is decomposed in the organism.

Tests for Colchicine.

From what has been already said, in testing for colchicine we must look for it in the fæces, in the contents of the large intestine, and in the urine. The poison may be separated from these organic substances by acidulating with dilute sulphuric acid, and digesting them for a long time with alcohol. After filtration the alcohol must be distilled off, and the residuum shaken with benzine or chloroform, or a mixture of both. When these fluids are evaporated, the colchicine remains behind in sufficient purity to be used for reactions. Chloroform extracts other substances besides colchicine from organic mixtures, and so does benzine, but in a much less degree. We can, therefore, especially when testing for it in the urine, first extract the alcohol-residuum with chloroform, then withdraw and evaporate that, and extract the remaining residuum with benzine, and this, when it is evaporated, leaves the colchicine purer than the chloroform does (Dragendorff and Speyer).

The evidence of the presence of colchicine rests chiefly on the yellow color it gives with hydrated sulphuric acid and the color test with nitric acid. Hydrated sulphuric acid gives a yellow color, clearly discernible, according to Dragendorff, even in one-twelve-hundredth of a grain (one-twentieth of a milligramme); the nitric acid reaction is discernible in one-three-hundred and thirtieth of a grain (one-fifth of a milligramme). This latter test depends on the fact that nitric acid—specific gravity 1.4—dis-

solves colchicine with the development of a violet color, passing into blue and then into yellow. Dragendorff recommends the application of both tests in the following manner: he dissolves the substance containing the colchicine in eight minims of hydrated sulphuric acid, and allows it to stand about twenty-four hours under a bell-jar, and then he adds to it one drop of nitric acid of 1.3 to 1.4 specific gravity. The fluid immediately becomes of a green color, then blue, violet, and finally pale yellow. This test, thus applied, gives a characteristic reaction, even in one-seven-hundredth of a grain (one-tenth of a milligramme).

Frogs are very little sensitive to the action of colchicine, so that the physiological test which these animals afford in most cases of poisoning by the organic alkaloids fails us here, for even with a fatal dose (about ten miligrammes = one-sixth of a grain) they present no very characteristic symptoms.

Poisoning with Helleborin and Helleborein.

Several species of hellebore contain the glucosides helleborin and helleborein in varying quantity; among these are Helleborus orientalis, ponticus, viridis, fœtidus, niger, purpurascens, and their varieties.

Schroff,[1] and more recently Marmé[2] and A. Husemann, have been chiefly concerned in investigating the alkaloids contained in these plants, and in examining and isolating them.

Schroff first examined thoroughly the action of the different species of hellebore, and found in them two distinct poisons, one an acrid and the other a narcotic principle; he obtained a preparation in the form of a watery extract which contained more of the narcotic imgredient, while with alcohol he extracted the acrid principle in considerable quantity, and he proved that Vauquelin's helleborin differs from that of Bastik.

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[1] Präger Vierteljahrschrift. LXII. p. 49. 1859. und LXIII. p. 95. 1859.

[2] Zeitscrift für rationelle Medicin von Henle und Pfeuffer. III. Reihe. Bd. XXVI. 1865. pp. 1–98.

A. Husemann and Marmé succeeded in separating these substances in a pure state from Helleborus viridis and niger.

According to them, *helleborein* is an inert non-nitrogenous substance; it is a glucoside, has a sharp taste, excites sneezing, is deliquescent and darkened by exposure to the air, is readily soluble in water and proof spirit, but almost insoluble in ether. When heated with sulphuric acid, it decomposes into sugar and a violet-colored substance in a moist condition, helleboretine.

Helleborin consists of white, glistening, acicular crystals, which are tasteless, and in solution produce a burning sensation in the mucous membrane of the mouth. It is sparingly soluble in water and ether, readily so in alcohol and chloroform. It decomposes into sugar and another substance, helleboresin.

The plants which contain these substances were frequently the cause of poisoning in former times, especially from persons eating the powdered root or swallowing a decoction prepared medicinally from them. We have absolutely no reports of similar cases in modern times.

The *symptoms* which these poisons give rise to in the human subject mainly affect the nervous centres: swimming in the head, stupor, giddiness, singing in the ears, uneasy sleep, sometimes a state of sopor; to these succeed symptoms affecting the circulatory system, diminution of cardiac pulsation, loss of cardiac power, distress, anxiety, weariness; then follow certain disturbances of the alimentary tract, as increased secretion of the saliva, violent pains in the stomach and intestine, vomiting, sometimes diarrhœa. Death is caused by cardiac paralysis, and is preceded by collapse; this last symptom is partly dependent on the vomiting and the diarrhœa; these, especially in the case of small doses frequently administered, frequently set in violently, showing a decidedly cumulative action of the poison. The pupils are sometimes dilated, sometimes they are unaltered.

Hellebore-poisoning, as thus described, results from the joint action of the two active principles contained in the plant.

Helleborein acts chiefly upon the heart, in the same way as digitalis, but more powerfully; the heart-stroke is retarded, and only becomes accelerated immediately before the approach of death; the blood-pressure is at first increased, as in the case of

digitalis, but afterwards diminished; respiration becomes slow and labored, but continues after the heart has ceased to beat. Convulsions are rare; the pupils remain unaltered.

Helleborin, on the other hand, creates great excitement and restlessness, succeeded by paralysis of the lower extremities; this paralysis may extend over the whole body and pass into profound stupor and general anæsthesia. The pupils are dilated by helleborin.

Both poisons act similarly upon the intestinal canal, producing salivation, vomiting, diarrhœa, etc. Helleborus niger acts in the manner described above; Helleborus viridis produces more intestinal symptoms than the Helleborus niger; Helleborus orientalis has the strongest effects; Helleborus fœtidus is less powerful, but more so than Helleborus niger (Schroff).

It is remarkable that in autopsies we find no signs of gastroenteritis; hyperæmia and even hemorrhage are often found in the brain; the spinal marrow also is often injected, its resistance appears to be diminished, and it is often the seat of extravasations (Marmé).

Both substances are absorbed from the mucous membrane of the stomach, and are probably separated unchanged by the urine. When poisoning is suspected, the matters vomited and the contents of the stomach must be the principal objects of chemical investigation. This poison, and especially helleborein, can be extracted in a tolerably pure form from its organic admixture by dilute sulphuric acid, and by subsequently shaking with chloroform or amylic alcohol.

This, when sufficiently pure, if treated with concentrated sulphuric acid, gives almost immediately a beautiful red color, which gradually becomes violet; but if it is impure it may easily be confounded with digitalein, with which it has many properties in common.

The *physiological test* of helleborein depends on the fact that in a frog poisoned with it cardiac pulsations become gradually slower, and, generally without the occurrence of any irregularities in the cardiac contraction, the heart, after a short time, is arrested in diastole. The cardiac muscle, however, remains for some time sensitive to direct irritation. It is evident from what

has been said that the physiological test for this poison is by no means very characteristic.

Poisoning with Aconitine and Plants containing it.

In the year 1833 Geiger and Hesse obtained aconitine from the herb Aconitum Napellus, and Planta gave the following formula for it: $C_{30}H_{47}NO_7$. All other species of aconitum contain the same alkaloid, only in varying quantities. Aconitum lycoctonum, according to Huebschmann,[1] is the only species that contains no aconitine, but another alkaloid, lycoctonine. But plants containing aconitine contain also another alkaloid; thus Huebschmann discovered *acolyctine*, and T. and H. Smith discovered another base, viz., *aconelline*, in Aconitum Napellus; and the latter, according to Jettelet, is identical with narcotine.[2]

Chemists distinguish German, English, and French aconitine, according as they are prepared from different varieties of napellus, and these contain other substances besides aconitine. *German aconitine* has not always the same properties, but varies according to the different manufactories and modes of preparation. It is generally colorless, amorphous, free from odor, and unaltered by exposure to the air. It has a very bitter taste, and leaves a burning sensation in the throat. This burning sensation varies in degree, according to the different preparations. It has a strong alkaline reaction, is sparingly soluble in water, readily so in alcohol, ether and chloroform, benzol and amylic alcohol.

The *English aconitine*, which is prepared by Morson by a process which is kept secret, is also called pure aconitine or napelline, and differs in several points from the German, which is more like the French. Morson's aconitine is generally a white granular substance, without decided crystalline structure; it is less readily soluble in alcohol and chloroform than the German, and has a sharp, but not bitter, taste. The English aconitine is

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[1] See *Husemann*, Die Pflanzenstoffe, etc. p. 211.
[2] See *Husemann*, Ibid.

a much stronger poison than the German; indeed, it is essentially different from it in its quantitative action. Duquesnel was the first who obtained a crystalline form of aconitine; he assigned to it the formula $C_{27}H_{39}NO_{10}$. This crystalline aconitine is most probably also contained in the non-crystalline preparations.

Etiology.

Aconitine-poisoning may arise either from the alkaloid itself, or from the leaves, flowers, or roots of the various species of aconite (in Germany the most important is the Aconitum Napellus), and the preparations, extracts, etc., prepared from these plants, when introduced in sufficient quantity into the system. The maximum dose of aconitine, according to the new German Pharmacopœia, is 0.004 (one-seventeenth of a grain) per dose, and 0.03 (nearly half a grain) per diem. Of the extract of aconite, the largest dose is three-eighths of a grain, and a grain and a half per diem, for medical purposes. Doses of three-quarters of a grain of aconitine may, however (Husemann[1] gives a case in point), be given for several consecutive days without any mischievous results. Schroff[2] has shown that six grains of aconitine in alcoholic solution was not fatal to rabbits, but as much as twelve grains in twenty-four hours was required to kill them. Tolerably large doses of extract of aconite may also be taken without fatal consequences, as appears from the researches of Schneller and Flechner,[3] who took as much as 26½ grains, without destroying life, though symptoms of poisoning occurred. Of Duquesnel's aconitine, one-thirteen-hundredth of a grain was sufficient to paralyze a frog, and one-seventieth of a grain to kill a rabbit. Cases of poisoning by the various species of aconite are mostly observed in England; in Germany they

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[1] Handbuch der Toxikologie. p. 571.

[2] Journ. f. Pharmacodynamik. I. 3. 1857.

[3] *J. Schneller*, Pharmacolog. Studien. Zeitschr. der Wiener Aerzte. März, 1846. p. 398 ff.; and *Schneller* and *Flechner*, Beiträge zur Physiologie der Arzneiwirkungen. I. Zeitschr der Wiener Aerzte. Mai, 1847.

are rare, still they do occasionally occur. Koch[1] communicates a case of a powerful man, 30 years of age, who died in three hours from partaking of a porridge of meal and aconite roots, which had been mistaken for horse-radish.

A child[2] two years and seven months old ate some aconite leaves, and died very rapidly with symptoms of intestinal inflammation. Dr. Ogier Ward[3] describes a case in which a family was poisoned, also by mistaking the roots of Aconitum Napellus for horse-radish. A woman was preparing mixed pickles, and her daughter added one pound of aconite root to them instead of horse-radish. All four persons recovered, but not without having been seriously ill. Tincture of aconite has also led to poisoning of a more or less violent nature. A case of suicide[4] by tincture of aconite is also on record, which ended fatally in five hours. In a case described by Strecker,[5] a man fifty-seven years of age, who was suffering from asthma, took a teaspoonful of tincture of aconite and died in two hours. A series of cases of poisoning with Aconitum ferox occurred in Constantinople in the following manner: Aconite root had in Calcutta been mistaken for jalap root, and sent as jalap to Constantinople,[6] where it was used as aperient medicine. Johnson[7] reports the case of a man who mistook tincture of aconite for some alcoholic beverage, drank perhaps the equivalent of a teaspoonful, and died in consequence. A similar case is given in the *Pharmaceutical Journal*,[8] in which an apothecary's man died in two hours from taking an unknown quantity of tincture of aconite. We have also an account of a family of five persons who partook of some salad into which aconite root had been introduced instead of celery;[9] two of them died in three and a half hours. A woman suffering

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[1] Würtemberg med. Corresp.-Blatt. No. 35. 1856.

[2] Accidental Poisoning by the Leaves of Monkshood. Lancet. June, 1856.

[3] Brit. Med. Journ. Dec. 1, 1860.

[4] The Lancet. May, 1855.

[5] Edinburgh Med. Journ. VII. p. 259. Sept., 1861.

[6] *Schroff*, Zeitschr. des Oesterr. Apotheker Vereins. III. p. 173. 1865.

[7] Lancet. Feb. 1867.

[8] Sept. 181. 1868.

[9] Journ. de Chim. Med. Mai. p. 248. 1868.

from acute rheumatism[1] took internally a mixture of chloroform and tincture of aconite, which was intended for external application, and was poisoned. Dobie[2] has reported the case of a veterinary surgeon, who, in a state of intoxication, took an ounce of tincture of aconite (Fleming's tincture), and recovered, whereas the same dose killed a man-servant.[3] In addition to all these cases, there is a series of cases of poisoning recorded which took a favorable turn, and ended in recovery. One of these, reported by Easton,[4] refers to an attempt to commit suicide by means of three drachms of Fleming's tincture of aconite; in this case, recovery followed the use of emetics. Brown[5] also describes the case of a woman thirty-one years of age, who took by mistake twenty-five drops of fluid extract of aconite; very severe symptoms of poisoning followed; still the woman recovered. J. St. Clair Gray[6] reports another case, of a nurse who took by mistake a little over one drachm of tincture of aconite, and recovered, notwithstanding very violent symptoms. It would seem that much larger doses of tincture of aconite than this may be taken without danger, from Turchetti's[7] and Nelaton's[8] recommending it, in doses of from half a drachm to a drachm,[9] in pyæmia. The case of criminal poisoning by Dr. Pritchard, in 1865, by means of a mixture of tincture of opium and tincture of aconite, is worth mentioning.

Symptomatology and Course.

The most accurate observations upon the subjective and objective symptoms produced by moderate doses of aconite have been made by Fleming[10] and Schneller and Flechner (loc. cit.).

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[1] Pharmac. Journ. and Transact. 1870, p. 307.

[2] Brit. Med. Journ. Dec. 22. p. 682. 1872.

[3] Brit. Med. Journ. No. 23. p. 579. 1873.

[4] Lancet. II. No. 2. p. 34. 1866.

[5] Boston Med. and Surg. Journ. July 21, 1870.

[6] Glasgow Med. Journ. Aug. 492. 1870.

[7] Gazetta Sarda. 25. 1857.

[8] Gaz. des Hôpit. 29. 1857.

[9] It is hardly necessary to say that no such doses could be allowed of the U. S. tincture, and they would be excessive even of the weaker British tincture.—E. C.

[10] Ueber die physiolog. u. therap. Wirkungen des Eisenhutes. Oesterr. med. Wochenschr. p. 399. 1846.

Fleming observed as the result of small doses—single drops, for instance—of the tincture, a sensation of heat and nausea, gastric oppression, rigidity of the muscles and formication, muscular weakness, swelling of the lips and tongue, lassitude, diminished frequency of pulse and respiration. The duration of these symptoms is from one to three hours. With larger doses, about ten drops, sensitiveness of the skin was diminished, pulsation and respiration still more; then followed giddiness, coldness of the extremities, and this condition lasted from three to five hours, torpor continuing still longer. Fifteen drops of tincture of aconite destroyed the sensitiveness of the skin, produced great anxiety, feebleness of voice and of power of motion, a reduction of the pulse to 40–36, which at the same time became feeble, small, and irregular; then fainting-fits set in, while the respiration was either rapid and superficial, or slow, deep, and spasmodic. This condition lasted between one and two days.

Still larger doses produced collapse, cold clammy perspiration, loss of hearing, sight, and speech, dilatation of the pupils, trembling and cramps of the extremities, and fainting-fits, followed by death. Schneller and Flechner made experiments on themselves, taking from ½ a grain to 26½ grains of extract of aconite. The symptoms produced were violent eructation, dull headache, and, even with small doses up to 5 grains, diminution of the alvine evacuation. With larger doses, up to 10 grains, there followed distention of the abdomen, dryness and tickling in the throat, depression of spirits, disturbed sleep, acceleration of the pulse, and palpitation of the heart. With 20 grains and upwards, the abdominal symptoms and the headache were aggravated, the tonsils became swollen, pains in the back and in the region of the heart came on, and there was failure of memory, etc.

The symptoms which attend cases of real poisoning are generally the following:

In many cases, especially when tincture of aconite has been taken, inflammation of the mucous membrane of the mouth appears; this is followed in most cases by pricking, numbness, and paralysis of the tongue; articulation is often very difficult; pain in swallowing and swelling of the tonsils have also been observed;

and frequently there is salivation. Vomiting and other functional disturbances follow. The cardiac pulsations are retarded—thus O'Connor[1] has recorded a case in which the pulse was reduced to 40–20 in the minute—and at the same time it becomes feeble, thread-like, and finally irregular; the heart-stroke becomes fainter and fainter, and scarcely audible. The cardiac symptoms last a considerable time, for Evans,[2] even the day after he had given three-quarters of a grain of extract of aconite root to an emphysematous patient, could only count 55 pulsations, and that after the more violent symptoms had disappeared for three hours.

In slighter cases the respiration does not seem to be much affected, at most somewhat accelerated; but in severe cases the respiration becomes less and less frequent, irregular, and sighing; in the most severe cases it fails entirely. The temperature of the body is lowered, at least at the periphery; coldness of the features and cold clammy perspiration are invariably observed.

The patient constantly complains of great muscular weakness; slight muscular rigidity is apparent to the patient as well as to the physician. At the same time, certain muscles may be convulsed, *e. g.*, the facial muscles or some muscles of the extremities. Actual tonic convulsions have been very seldom observed, and when they occurred, as in one of the cases mentioned by Ozier Ward, they were probably dependent on other circumstances; the convulsions which immediately precede death are to be regarded as consequences of the supervention of carbonic acid poisoning; the feebleness of the voice and respiratory organs may also be connected, at least partially, with the muscular weakness.

As a rule, consciousness is undisturbed, although headache, more or less violent, is never absent; the marked anxiety does not depend on the action of aconitine on the brain, but is due to the disturbances of respiration and circulation. Delirium has certainly been observed in a few isolated cases, but so rarely that it cannot be attributed directly to the aconite. Affections of the

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[1] Dublin Quart. Journ. Feb. 1857.

[2] Brit. Med. Journ. Sept. 21, 1861.

sight are very constantly reported: dimness or mistiness of vision, temporary amaurosis, amblyopia, partial blindness, etc., with dilated pupils, which are scarcely ever absent.

In the abdominal region the most constant symptom is violent pains in the stomach; severe colicky pain has been very rarely observed, and diarrhœa still more rarely, but constipation is frequent. Micturition is in almost all cases arrested during the action of the poison.

The symptoms of poisoning follow very soon after the introduction of aconitine into the system, or portions of the plants or preparations containing it. When the poison is injected directly into the blood of animals, death ensues in a few minutes. In human subjects the effects of the alkaloid introduced through the mouth usually set in in the course of half an hour, as in Evans's and Easton's cases, seldom sooner or later. The duration of the poisoning is usually very short. Cases[1] are known in which death occurred two, three, or five hours after the introduction of the poison. Recovery is also tolerably rapid in most cases: in Brown's case in four hours, in O'Connor's in three hours. When the case takes a favorable turn, the hopeful symptoms set in pretty soon; in Evans's case after three hours. The recovery is generally complete, for the sensation of muscular weakness, the retardation of the pulse, headache, etc., last only a few hours after the more violent symptoms; only the tingling in the tips of the fingers and in the tongue sometimes lasts rather longer.

Analysis of Symptoms.—Character of Aconitine Poisoning.

The striking effect upon the mucous membrane of the mouth and nose, the salivary glands, and the mucous membranes of the stomach, depends upon direct irritation of the sensory nerves and the vessels of the parts affected by the acrid poison. As this acrid principle is present, in varying proportion, in the different plants, and parts of plants, and also in the various preparations of aconite, therefore this effect is not always equally observable

[1] *Dr. Strecker*, Edin. Med. Journ. VII. p. 259. Sept., 1861.

in all cases of poisoning. The vomiting is most probably a reflex action, dependent on the irritation of the sensory nerves of the stomach.

The main effect of aconitine and the actual cause of death is its influence upon the action of the heart. Experiments made on animals show that even in their case, as a rule, diminution of the frequency of cardiac pulsation, loss of power, and irregularity of cardiac contraction, follow the administration of small as well as large doses. According to Achscharumow[1] the vagus is first centrally excited by the German aconitine, and the cardiac pulsation consequently retarded; this statement is, however, questioned by Boehm and Wartmann. Subsequently, the terminations of the vagus are paralyzed, and an increase in the frequency of the heart-stroke would necessarily follow if the intrinsic motor cardiac nerves had not themselves meanwhile become paralyzed. Later on, however, the cardiac muscle itself appears to be paralyzed, since, according to Boehm's experiments, there was a stage in which stimulation of the heart at its apex failed to excite contraction. According to Boehm's[2] researches, the ventricle in frogs is much more strongly affected and much more rapidly paralyzed than the auricles, which remain excitable for some time longer. Boehm also asserts that minimum doses from one-seven-hundredth to one-seventieth of a grain given to frogs at first produce increased frequency of the heart-stroke, about 10–30 beats; but he, like Achscharumow, observed a subsequent retardation, which began with a cramp-like arrest of cardiac action, and passed into complete paralysis. According to Boehm, therefore, aconitine first excites the cardiac motor centre, then paralyzes the inhibitory centres, but at the same time also the excito-motor ganglia and the cardiac muscle itself. The results of this cardiac paralysis are naturally dyspnœa and carbonic acid poisoning, with convulsions. The blood-pressure is increased at the outset of the poisoning, but later on it is found to be constantly lowered, which is in accordance with the action on the heart. Respiration is constantly retarded

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[1] Arch. f. Anat. u. Physiolog. p. 255. 1866.

[2] Ueber Herzgifte. p. 20 ff.

by aconitine. It is not yet decisively proved whether this is the effect of paralysis of the extremities of the vagus in the lungs, or of paralysis of the respiratory centre in the medulla oblongata, or of both combined. It is most probable that the respiratory centre is paralyzed; for the retardation of respiration is chiefly dependent on the state of the muscles of respiration, and they, like the rest of the striped muscles, are directly affected by aconitine—that is to say, the extremities of their motor nerves are paralyzed by this poison as by curare, as appears from the investigations of Leonidas van Praag,[1] Schroff,[2] Liégeois, and Hottot.[3] Boehm and Wartmann,[4] on the contrary, never succeeded in finding paralysis of the extremities of the motor nerves, whereas they did observe fibrillar twitchings of the muscles, which they attributed to excitement of the intermuscular extremities of the nerves. The reports on the influence of aconitine on the sensory nerves differ from one another in the most essential points, and it is probable that these contradictory results with regard to this point, as well as with regard to the action of aconitine on the heart and the muscles, were dependent upon the difference of the preparations employed in the experiments. The most important and most obvious symptoms which are observed clinically in cases of poisoning are alterations in cardiac action, in respiration, and in the condition of the striped muscles, and these are accounted for in a tolerably satisfactory manner by what has been said above. The lowering of the temperature, the subjective symptoms, anxiety, etc., are explained by the altered circulation. Death caused by aconitine is distinctly due to its effect upon the heart, as is proved by the series of symptoms observed in the human subject and by experiments on animals.

The dilatation of the pupils observed in many cases of poisoning is probably not directly dependent on the action of aconi-

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[1] Virch. Arch. p 458 ff. 1855.

[2] Wochenbl. d. Zeitschr. d. Gesellschaft. d. Aerzte zu Wien. No. 18. 1855. und Prager Vierteljahrschrift. 1854. XI. 2.

[3] Journ. de Physiologie. IV. p. 520. Oct. 1861; and *Hottot*, Journ. de l'Anat. et de la Physiolog. Mars. 113. 1864.

[4] Verhandlungen der phys. med. Gesellsch. in Würzburg. N. R. III. 63.

tine, but is possibly only a symptom of carbonic acid poisoning; at least, we cannot succeed in producing dilatation of the pupil by direct application of aconitine to the conjunctiva.

Results of Autopsies.

We possess a number of reports of autopsies in cases of fatal aconite-poisoning, but they are so much at variance with each other that it is impossible to find in them characteristic phenomena. Thus Koch found the face red and swollen, whereas others have discovered a remarkable pallor and bloodlessness over the whole surface of the body. In many cases the lips and the mucous membrane of the throat are found to be destitute of epithelium; very often the mucous membrane of the mouth and throat is remarkably red; this hyperæmia also extends to the stomach; of course, these appearances are only found when the poison has been introduced through the mouth. Some have observed a hyperæmia of the brain and its membranes, which in a few cases may lead and has led to extravasation. The lung is constantly found in a hyperæmic condition; fluid is sometimes found in the serous cavities; the liver, spleen, and kidneys are all engorged. In a large majority of cases the blood is reported to have been fluid, and uncoagulated; the color of the blood is in some cases cherry-red, in others darker. The heart is flaccid, and the right ventricle constantly full of blood. The small intestine is hyperæmic, with small patches of inflammation here and there, which in a few cases may have become gangrenous. The bladder is generally strongly contracted. Portions of the drug, small pieces of the root, etc., are sometimes found in the contents of the stomach and the intestine, and can be identified by their histological character. On the whole, the results of autopsies are altogether insufficient for the recognition of aconitine-poisoning.

Diagnosis and Differential Diagnosis.

It is very difficult to diagnose aconitine-poisoning by clinical observation alone, for although we may be convinced that it is a case of poisoning, yet there may be many difficulties in the way

of discovering what the poison actually is. The gradual diminution in the frequency of the pulse and of the respiration, together with difficulty of swallowing and speaking, may afford some ground for a diagnosis, and there is less disturbance of the sensorium than in cases of pure narcotic poisoning. The diagnosis is considerably facilitated if portions of the plant are found in the matters vomited, if the lips are excoriated, if the patient complains of formication, tingling of the tongue, etc. Great muscular debility is also an important symptom, as is mydriasis, though this is usually slight. Aconitine-poisoning, as distinguished from poisonings by other alkaloids, may be mistaken for poisoning with vegetable acids, or it may be confounded with cerebral disease.

Prognosis.

The prognosis is generally unfavorable if a considerable quantity of the poison has been absorbed ; of German aconitine from a grain and a half to a grain and four-fifths is considered to be a fatal dose, while, according to Taylor, much smaller doses of the English aconitine are sufficient to destroy life. The prognosis is most favorable when copious vomiting has set in early. As aconitine is one of the most active poisons, the prognosis is the more hopeful the longer the illness has lasted. If from six to eight hours have elapsed since the introduction of the poison, there is probability of recovery. If we succeed by treatment in improving the condition of the heart, this furnishes another important basis for the prognosis.

Treatment.

In the treatment of poisoning by aconite, the first thing to be done is to administer an emetic, or we may need to use the stomach-pump, to get rid of the poison not yet absorbed. At the same time, the ordinary chemical antidotes, namely, tannin and iodine, may be administered. But the most important point, at a later stage, is to treat the symptoms, and especially to give stimulants, to avert threatened cardiac paralysis; alcohol, ether, and cam-

phor are the best; irritants of the skin, electricity, etc., should also be employed. J. St. Clair Gray appears to have found the tincture of nux vomica useful, but as the dose which had been taken consisted only of seventy drops of tincture of aconite in one case and fifty in another, not absolutely fatal doses, and as wine and ammonium carbonate were employed at the same time, no decisive conclusion can be drawn as to the action of this drug. In Dobie's case, in which a veterinary surgeon had taken an ounce of Fleming's tincture of aconite, two drops of which killed a sparrow in three and a half hours, recovery was brought about, in spite of violent collapse, by the employment of emetics, electricity, and subcutaneous injection of thirty drops of tincture of digitalis.

Changes which Aconitine Undergoes in the Organism of Animals.

Aconitine, which is to a great extent soluble in the gastric juice, is, when taken into the stomach, in part absorbed into the blood and in part excreted with the fæces unchanged. This excretion by the intestine is tolerably rapid in the first instance, but in a later stage it is slow. Thus Dragendorff could detect considerable quantities of aconitine in the stomach and in the small and large intestine of a dog which had been shot seven hours after the introduction of four grains of aconitine. That portion of the aconitine actually absorbed circulates through all the organs, and the greater portion of it is finally excreted unaltered in the urine. Dragendorff succeeded in detecting the alkaloid in the blood, in the liver, in the kidneys, in the urine, and also in smaller quantities in the gall-bladder, in the lungs, and in the heart.

Chemical and Physiological Tests.

The best reaction by means of which aconitine can be detected when in a pure condition consists in dissolving the alkaloid in concentrated sulphuric acid, in which it at once dissolves with a

yellow color; if large quantities of it are present the fluid becomes brown in from one to two minutes, then changes gradually to reddish-brown, and finally violet-red, which last color gradually disappears, so that after about twenty-four hours the fluid is colorless. The violet-red color is observed, in the case of small quantities, within two hours—in larger ones not till after four or five hours. If we use a small watch-glass for this reaction, it is possible to recognize any quantity exceeding one-one-hundredth of a grain.

Aconitine is thrown down from its solution by molybdo-phosphoric acid, at first as a gray precipitate, which later on becomes bluish, and which is colored blue by ammonia. It is thrown down in solutions containing only one-one-thousandth of a grain of aconitine in one and two-thirds ounces of water. Tincture of iodine and chloride of gold and tannic acid also throw down aconitine.[1]

The physiological test of the poison depends on its effect on the frog. According to Achscharumow and Adelheim, the symptoms produced are paralysis of the hinder extremities, loss of reflex action in the lower half of the spinal marrow, then paralysis of the fore-limbs, and, finally, the heart is arrested in diastole.

The development of this series of symptoms, when one-seventieth of a grain of aconitine has been subcutaneously injected, may last several hours, but death frequently does not ensue for several days. In applying this test the aconitine is combined with acetic acid by moistening the dry alkaloid with that acid, drying it at 176° Fahr., and then dissolving it in water.

The separation of the poison from organic substances is effected, as in the case of other alkaloids, by extraction with water charged with sulphuric acid.

Shake the purified acidulated watery extract with petroleum ether, neutralize it with excess of ammonia, and then shake it as quickly as possible with benzine. The benzine, when evaporated, leaves the alkaloid in a state sufficiently pure for the chemical as well as the physiological test.[2]

Helwig[3] states that aconitine in small quantities, when care-

[1] *Dragendorff*, Beiträge, etc. p. 64. [2] For further details, see *Dragendorff*, l. c.
[3] Das Mikroskop in der Toxikologie. p. 61 ff.

fully heated, yields a sublimate consisting of granular particles mixed with little drops of oil, which is converted by vapor of ammonia into delicate acicular crystals, and by muriatic acid into beautiful little octahedral crosses and stars. All these crystals deliquesce very rapidly.

Poisoning with Delphinine and Plants containing it.

Delphinine, $\Theta_{24}H_{35}N\Theta_2$, was discovered in 1819 by Brandes, also by Lassaigne and Feneulle in the seeds of stavesacre (Delphinium Staphisagria), which plant contains also another alkaloid, namely, staphisagrine. Delphinine is probably present also in Delphinium Consolida (larkspur) and Delphinium Ajacis. It appears as an amorphous white mass, often presenting a resinous appearance. It has an alkaline reaction and a very acrid taste. It is sparingly soluble in water, more readily so in alcohol, ether, chloroform, and benzol.

The poisonous qualities of delphinine were established by Orfila by experiments on dogs. There are very few instances of human beings having been poisoned by this alkaloid, and the only case reported of poisoning by delphinine is one by van Hasselt, in which powder of stavesacre was taken instead of worm-powder.

The symptoms which this poison produces in animals are vomiting—coming on at a very early stage—retching, and diarrhœa; after a time disturbance in the organs of locomotion appear, namely, slight convulsions of the muscles of the extremities and of the jaw, later on lateral curvature of the body, diminished frequency of pulse, restlessness, and anxiety, and finally death from asphyxia, while the brain remains apparently unaffected.

All that is found in post-mortem examinations are the evidences of death by asphyxia, and sometimes eroded and inflamed patches on the mucous membrane of the stomach.

As regards the action of delphinine, it very much resembles that of veratrine and aconitine, so that it will be treated here

briefly as an appendix to aconitine, for its interest toxicologically is rather theoretical than practical.

The investigations of Falk and Roerig,[1] Leonidas van Praag,[2] Darbel,[3] Albers,[4] Cayrade,[5] Dorn,[6] and Boehm,[7] have been of essential service in elucidating the action of this poison. Delphinine promotes the salivary secretion, causes redness and inflammation of the palate, a burning sensation in the pharynx, and nausea and vomiting from violent irritation of the sensory nerves of these parts. Constipation of the bowels and difficulty of micturition are generally present (Albers, Schroff[8]). These last symptoms depend on the action of the poison excreted in an unchanged form by the urine and the fæces on the mucous membrane of the bladder and the intestine, and probably in a reflex manner on their muscular coat.

When applied to the nasal mucous membrane, delphinine excites sneezing; applied to the conjunctiva it produces conjunctivitis; on the cuticle an itching and burning, redness, and a kind of goose-skin (Turnbull).[9]

Its chief action is on the heart. The researches of Falk and Roerig, L. van Praag, and Boehm show that it produces cardiac paralysis by acting on the cardiac muscle, its excito-motor nerve-centres and the inhibitory apparatus, so that (after a temporary initial increase of the frequency of pulsation) a steady reduction in the number of the cardiac contractions ensues. This is followed and accompanied by disturbances of the respiration (dyspnœa). At the same time, as Cayrade especially states, a paraly-

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[1] Das Delphinin und das Pflanzengenus Delphinium. Arch. f. phys. Heilkde. 528-548. 1852; and *Roerig's* Dissert., De effectu Delphini. Marburg. 1852

[2] Toxicologisch pharmakolog. dynamische Studien über Delphinin. Virch. Arch. Bd. VI. 385-408 und 435-457.

[3] Recherches chimiques et physiologiques sur les alkaloides du delphinium staphisagria. Montpellier. 1864. Thèse.

[4] Allg. Zeitschr. Psych. XV. 348. 1858.

[5] Sur l'action physiologique de la delphine. Journal de l'anat. et de physiolog. Mai et Juni. 317. 1869.

[6] De Delphinino observat. et experiment. Bonn, 1857. Dissert.

[7] Studien über Herzgifte. 1871. p. 52 ff.

[8] Pharmakologie. 3 Aufl. p. 547.

[9] On the Medical Properties of the Natural Order Ranunculaceæ. London, 1835.

sis of reflex action is apparent. In this process the poison most probably produces a paralysis of the spinal marrow ; but the muscles are also in a high degree sensitive to the action of delphinine, and they also are paralyzed by it, and so contribute to the diminution of reflex activity. This observation has led some to conclude that the excitability of the peripheral sensory nerves is also diminished—an inference which is certainly premature. This reflex paralysis extends from behind forwards, and the paralysis of the spinal marrow precedes that of the voluntary muscles (Cayrade). The diminution of the frequency of respirations depends mainly on the paralysis of the respiratory centre by delphinine ; but the general muscular paralysis, in which the respiratory muscles share, contributes essentially to the difficulty of respiration, and to its ultimate cessation.

With regard to the dose of delphinine which may prove fatal one-sixteenth of a grain is sufficient to kill a frog in a couple of hours ; dogs and cats require doses of from half a grain to a grain and a half.

A supposed case of poisoning should be treated at first with emetics ; remedies containing tannin might also be serviceable, for delphinine and tannin form a compound very insoluble. Lastly, treatment ought to be directed to arresting threatened cardiac paralysis.

Poisoning with Nicotine and Plants containing it.

Nicotiana Tabacum. Tobacco.

Tobacco—originally found in North America—was introduced into Europe and cultivated here about 200 years ago, and, since it possesses in a high degree poisonous properties of a narcotic order, it has, on that account, become a means of enjoyment to many, in the same manner as coffee, tea, alcohol, etc. In the various forms in which tobacco is used—snuff, tobacco for smoking, cigars, cigarettes, tobacco for chewing—it frequently leads to slight forms of poisoning. The active agent in tobacco is

nicotine, a very volatile fluid alkaloid, transparent as water, with an unpleasant, penetrating odor, and a strong, burning taste; it combines readily with water, alcohol, and ether; it assumes a brown color on exposure to the light; when long exposed to the air it becomes resinous. Nicotine is contained in different proportions in the various sorts of tobacco; according to Schloessing's statements, the best Havana tobacco contains only 2 per cent. of nicotine, while other sorts contain as much as 7 and 8 per cent. Other authors maintain that Schloessing's figures are too high. According to Dumas, tobacco contains about 1 part in 1,000 of nicotine.

Etiology.

Nicotine is contained in the different parts of the tobacco plant, but principally in the leaves, and these, with the productions manufactured from them, lead to the greatest number of poisonings. Nicotine easily makes its way into the fluids of the organism; if the alkaloid is placed directly on the tongue, in the course of a few seconds poisoning sets in; the process is almost as rapid when infusions of tobacco are taken internally—or, for example, when snuff is introduced into the stomach accidentally or intentionally; absorption from the rectum is also rapid, as has been repeatedly proved by poisoning from enemata of tobacco. Poisoning by tobacco may also occur through the unbroken cuticle, by the application of infusion of tobacco, or ointment of tobacco, or even by dry tobacco leaves.

Cases of poisoning by the internal administration of tobacco are not infrequent, and occur either through its being mistaken for other substances, *e. g.*, coffee,[1] or when it is used as an emetic,[2] for which purpose snuff is generally employed. Tobacco-chewing has led to poisoning in numerous cases. Although the tobacco used for this purpose, according to the experiments of Vohl and Eulenberg,[3] contains very little nicotine, yet so much

[1] Journ. de Chim. méd. Nov. 1866. p. 598.

[2] Oberstadt. Rhein. Monatsschrift f. pract. Aerzte. Oct. 1851.

[3] Vierteljahrschrift für gerichtliche Medicin. XIV. Heft 2; and Berliner klin. Wochenschr. 14. Aug. 1870. p. 395.

tobacco is consumed in chewing, that nicotine enough is swallowed to lead to poisoning. Among tobacco-chewers may be reckoned those smokers who half chew, half smoke their cigars, and indeed most cases of poisoning occur with smokers of this kind. Striking examples are recorded of absorption of nicotine through the external application of tobacco. We may not, perhaps, see anything very remarkable in cases of poisoning arising out of the use of the infusion of tobacco-leaves as compresses for wounds,[1] or from its application in the form of ointment in eczema,[2] but the case communicated by Namias,[3] in which a smuggler carried tobacco leaves on his bare skin across the frontier, and was violently poisoned by them, is certainly very striking. Ten cases from older authors are mentioned by Gallavurdin,[4] in which the outward application of tobacco led to poisoning, and Martin[5] witnessed a case of violent poisoning, arising from the use of a woollen compress soaked in a weak infusion of tobacco.

It is from smoking tobacco, however, that nicotine-poisoning chiefly arises. Even though the tobacco loses much of its nicotine in the preparation—drying, soaking, etc.—and though a great part of it is decomposed in the burning; moreover, though a large portion of the smoke does not come into contact with the mucous membrane of the mouth, nevertheless the *quantity* of tobacco consumed in this way does in many cases lead to poisoning. Many different factors are to be taken into consideration in tobacco-smoking. In the first place, the smoke of the tobacco itself contains nicotine, as Henkel[6] has directly demonstrated and maintained in opposition to Vohl and Eulenberg, who attribute the action of tobacco to the piccoline and pyridine bases which are formed when it is burnt. According to these two authors, the pyridine group is the main factor in poisoning.

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[1] *V. Meyern*, Nachtheilige Wirkung der äusserlichen Anwendung der Tabaksblätter. Preuss. Vereinszeitg. No. 2. 1844.

[2] *Blanchard*, Journ. de Chim. méd. Mai. 203. 1869.

[3] Gaz. des Hôpit. Vol. 84. p. 336. Séance de l'Académie des Sciences. V. 11 Juin. 1864.

[4] Compt. rend. de l'Académie des Sciences. T. 59. p. 262.

[5] L'Union médic. 29. 1863.

[6] Centralblatt f. d. med. Wissenschaften. Oct. 5. 1871.

These bases may perhaps have some influence in tobacco-poisoning, but the poisoning produced by tobacco-smoke must after all be regarded as nicotine-poisoning. Nicotine is, at least in part, volatilized, unchanged at the temperature at which tobacco burns, and is condensed again on colder parts; for instance, a great deal of nicotine accumulates in the lower part of pipes, and the remains of cigars are decidedly much more impregnated with nicotine than the parts fresh smoked; again, large quantities of nicotine, as well as the other oleaginous and resinous products, are present on the sides of the mouth-pieces of tobacco-pipes and the ends of cigars. This tobacco-juice has repeatedly led to poisoning, generally by accident during the cleaning of tobacco-pipes,[1] which manipulation should be very carefully performed. This tobacco-juice from pipes has also been used to procure abortion, and has destroyed both mother and child; this juice (called Tsefêx) is used by Orientals in skin-diseases, and has frequently led to poisoning, as Landerer[2] mentions. Cases of poisoning are also on record through the medicinal use of enemata of tobacco, which were formerly much in request. Poisoning in the present day by the medicinal use of tobacco is almost impossible, as scarcely any physician would now think of prescribing enemata of tobacco, etc. But in 1873 a quack caused the death of a woman by ordering an enema of tobacco.[3]

The greatest number of cases of poisoning, however, arise from tobacco-smoking. It is scarcely necessary to say that every youth who commences to smoke cigars is attacked with more or less violent vomiting. Nor is it only the inexperienced smoker who is in danger of poisoning; even practised tobacco-smokers are often made ill when they smoke tobacco of a kind to which they are not accustomed. Tobacco is least dangerous in the form of snuff, as the nasal catarrh produced by it leads to the immediate elimination of the poison. Pure nicotine has been used for criminal poisoning, as, for example, in the case of Count Bocarmé, who poisoned his brother-in-law G. Fougnies with nico-

[1] *E. g.*, *Marchant*, Journ. de Méd. de Bruxelles. Mai. 1865. p. 429.
[2] Schweizer Zeitschrift f. Pharmaz. No. 11. p. 72. 1868.
[3] Leipziger Apothekerzeitung. 1873. p. 43.

tine in the year 1850. Taylor[1] mentions several cases of criminal poisoning by means of snuff and tobacco for smoking. Tobacco has also been used for the purpose of suicide. As to the dose which may prove poisonous, much must depend on individual constitution and habit. There is perhaps no poison to which a man can so readily accustom himself as tobacco. Whereas a few puffs of a cigar or a pipe are enough to produce somewhat severe symptoms in a neophyte, experienced smokers can only be affected by very large doses. Still, even the most practised smokers may become the victims of acute poisoning, for it has often been found that an excess beyond the accustomed quantity may produce temporary indisposition. Two or three drops of nicotine are sufficient to produce a severe form of poisoning, and eventually to cause death. In Bocarmé's case a much larger dose was administered. From fifteen to thirty grains of snuff are sufficient to produce violent, it may be fatal, poisoning, if the snuff is not adulterated; in a case communicated by Schneider,[2] one drachm proved fatal.

The death of two brothers is recorded from the continuous smoking of seventeen or eighteen pipes.[3] Pereira[4] gives a case in which twelve drops of infusion of tobacco, administered as an enema, caused death, and Copland[5] states that half a drachm internally administered in the form of infusion proved fatal. Dessault[6] also saw a case in which the administration of tobacco-smoke in the form of an enema led to a fatal result. Daily experience proves that in close rooms tobacco-smoke may lead to slight symptoms of poisoning, even in the non-smoking occupants. As to the duration of tobacco-poisoning it is, in most of the slighter cases, short, and even in fatal cases death ensues somewhat rapidly. Gustav Fougnies died thirty seconds after the poison had been administered; in another case,[7] a man who had chewed half an ounce of tobacco survived for four days.

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[1] Seydeler's Bearbeitung. III. Bd. p. 252.
[2] *Husemann*, Toxikologie. p. 483.
[3] *Gmelin.* See Pereira-Buchheim's Heilmittellehre. II. Bd. p. 328.
[4] *Pereira-Buchheim*, Bd. II. p. 329; and Brit. and Foreign Med. Rev. Vol. XII. p. 562.
[5] Dict. of pract. med., art. Colic. Vol. I. p. 371.
[6] See *Husemann*, Toxikologie. p. 482.
[7] Pharmazeut. Journ. Feb. 1868. p. 396.

Pathology.

Symptoms and Course.

When nicotine in sufficient quantity to produce poisoning has passed into the blood, the symptoms set in with some rapidity; in slight cases they usually succeed in regular order, but in more severe ones they succeed one another so rapidly that they can hardly be distinguished in order of time. The unpractised smoker usually becomes deadly pale, with distorted features, perspiration breaks out on the forehead and hands, the pulse becomes feeble and slow, the respiration is slow and labored; there is great anxiety, with giddiness, faintness, and a tottering gait, to which must be added salivation. These symptoms are very often accompanied with retching and vomiting, pains in the epigastric region, and actual colic, succeeded by diarrhœa. As a rule, the collapse does not last very long; in slight cases of poisoning it is the closing symptom; at the worst, headache, want of appetite, above all, disgust of tobacco-smoke, remain for some time. When we have to do with larger doses of the poison attacks of syncope occur, accompanied with complete unconsciousness, a small, compressible pulse, and very labored respiration. In this condition the contents of the rectum and bladder are often passed involuntarily. In the most severe cases tetanic convulsions supervene: there is prolonged collapse, with gradual failure of the pulse and respiration, and finally death.

To this general description in some few cases special symptoms must be added. The difficulty of breathing sometimes amounts to actual asphyxia, or the case may begin in this way, as in the one mentioned by v. Meyer, and already quoted. Hiccup also occurred in that case; sometimes the diarrhœa is accompanied with loss of blood, especially when tobacco has been taken internally. Deutsch[1] communicates a case of this kind, in which a man, in order to expel a tape-worm, had taken about an ounce of tobacco-juice; in this case, as in many others, the power of speech was to some extent impeded. Sometimes the

[1] Eine Vergiftung durch Tabak. Preuss. med. Vereinzeitg. No. 8. 1851.

effects of the poison begin suddenly; the poisoned person falls prostrate, as in Bocarmé's case, and in another case [1] of a man who had chewed half an ounce of tobacco. The tetanic convulsions may be absent even in very severe cases, *e. g.*, in the case reported by de Brieret,[2] in which a woman had been in the habit of smoking and chewing tobacco and taking snuff for four years, and who unexpectedly died rather suddenly from tobacco-poisoning.

In the early stage of poisoning it is generally found that the pupils are at first contracted and subsequently dilated; in some cases the power of vision is lost for a time; severe strangury has also been observed. The effects which result from the continued use of tobacco on many persons deserve special mention. There are writers who vehemently denounce its use, and attribute all imaginable evil consequences to it. The best evidence that tobacco does not generally produce such injurious effects lies in the fact that, in all places where tobacco is to be had, rich and poor make use of it with enjoyment. No smoker will doubt, what no non-smoker can conclusively disprove, that when tobacco is used in moderation, it may act very beneficially, and be a valuable source of human enjoyment, that it is almost indispensable to some people, and that it helps them considerably in the fulfilment of their duties in life. We do not mean to deny that the use of tobacco may have, and very frequently has had, injurious results. It has been questioned whether chronic poisoning is the result of a long course of tobacco-smoking, or whether it is a rapid succession of acute poisonings which produce the development of so-called chronic tobacco-intoxication. Our own view is that the diagnosis of chronic nicotine-poisoning depends on the development of a series of symptoms of disease dependent on the continued use of tobacco. In the first place, functional disturbances of cardiac action are frequently observed in constant smokers, although it is very doubtful if, as Kennedy[3] thinks, fatty degeneration of the cardiac muscle can be pro-

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[1] Pharmaceut. Journ. Feb. 396. 1868.

[2] Gaz. des Hôpit. 21. Juillet. 1864.

[3] Dublin Med. Press. Apr. 20, 1864.

duced by long-continued tobacco-smoking. Still, cases are not uncommon in which palpitations, with slow and intermittent action of the heart, give rise to much suffering. Thus Decaisne[1] observed in the cases of twenty-one passionate smokers intermission of the pulse and of the cardiac beat, without any detectable organic disease of the heart. To this are added a sensation of giddiness and faintness, uncertainty and trembling of the legs, disturbances in the co-ordination of movements, great muscular exhaustion, sleeplessness, and depression of spirits. According to Melier,[2] workmen in tobacco-manufactories suffer from these and similar symptoms, and gradually acquire a pale yellow cachectic appearance.

Tobacco also exercises a disturbing influence on the sense of sight. Apart from the fact that aggravated myosis sometimes sets in, as in Babington's[3] case, cases of actual blindness have occurred from chronic tobacco-poisoning. Thus Wordsworth[4] observed in three cases of tobacco-poisoning (in one case 1½ lb. had been smoked every week for a series of years) amaurosis, produced by white atrophy of the optic nerve. Hutchinson[5] has proved statistically that out of thirty-seven cases of amaurosis, resulting from white atrophy of the optic nerve, thirty-one occurred in immoderate smokers.

It is well-known that inveterate smokers very often suffer from gastric catarrh, cardialgia, constipation, or diarrhœa, and it is upon the disturbances of the digestive functions arising out of nicotine-poisoning that some authors found their theories of the tissue-changes to which this poison leads, but even Hammond's[6] researches on this subject have not been carried out with the precautions necessary. Hyperæsthesia in different nerves may be mentioned as a peculiar and rare effect of tobacco-smoking. Thus, for example, Schotten[7] observed in immod-

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[1] Compt. rend. Tome 58. p 1017. 1864.

[2] L'Union. 46. 1867.

[3] Dublin Journ. of Med. Science. p. 545. Nov. 1866.

[4] Lancet. 1863. July 25.

[5] Med. Times and Gaz. 28. Sept. 1867.

[6] The Physiological Effects of Alcohol and Tobacco upon the Human System. Americ. Journ. of the Med. Sciences. Oct. 1856.

[7] Virchow's Archiv. Bd. XLIV. 72. 1868.

erate smokers affections of the auditory nerves, of the optic and olfactory nerves, pains in the course of the plexus brachialis, in the intercostal nerves, in the pudendal nerve, with strong and painful erections. On the other hand, a remarkable abatement of the sexual instinct has been observed.[1]

The use of the cigar and the pipe has also been put forward as a cause of cancer of the lip; Stugocki[2] states that the chronic irritation acts chemically as well as mechanically, in producing local carcinosis. A case communicated by Fageret[3] goes to prove that inflammation and ulceration of the lips can be excited by persistent smoking; a gardener who smoked cigars made of tobacco of his own growing was attacked with ulcers of the lips, gray in the centre, and red at the edges.

Other authors assert that there have been many cases in which all the intellectual faculties have suffered, and even madness and other mental disturbances been produced, by immoderate and long-continued tobacco-smoking. But none of these statements have been established on a strictly scientific basis.

It is certain, however, that chronic nasal and pharyngeal catarrh may and very often do set in as a consequence of smoking and taking snuff; and, moreover, that laryngeal catarrh and bronchial catarrh may be aggravated by smoking and remaining in places used for smoking; there have been also some cases of co-called spinal irritation, or male hysteria, traceable to immoderate indulgence in tobacco. There are no veritable sequelæ either from acute or chronic nicotine-poisoning; but after the former, gastric disturbances may be observed for a short time, while in chronic poisoning a certain muscular weariness and weakness may last for a long period. In Deutsch's case, quoted above, in which a man had taken an ounce of tobacco-juice, and so became violently poisoned, years passed before he became completely restored to health. Frequently, hoarseness, pains in the hips and loins, or feeling of tension of the abdominal muscles, etc., remain for some time.

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[1] *E. g.*, *Höegh*, N. Magaz. for Laegevidensk. XXII. p. 62. 1868; and *Th. Clemens*, Deutsche Klinik. 26 and 28. 1872.

[2] Du tabac, son influence sur la santé et les facultés intellectuelles. 1867. Thèse. Paris.

[3] Du tabac, son influence sur la respiration et la circulation. Thèse. Paris. 1867.

Analysis of Symptoms.

A series of physiological researches lie before us, the results of which give us some insight into the action of nicotine, and enable us to comprehend, at least in part, most of the symptoms observed in cases of poisoning by this agent.

With regard to the action of nicotine upon the heart, the regular administration of small doses to animals is followed by a marked retardation of the heart-stroke, which, as Traube[1] showed in the dog, and Rosenthal[2] in the frog, proceeds from irritation of the cardiac extremities of the vagus. This effect is observed just the same after section of the vagus, but not when the animals have been previously curarized. Later on, the frequency of cardiac pulsations is restored; this depends on initial paralysis of the extremities of the vagus, for if we now irritate the vagus, we fail to produce diminution of the cardiac beats. According to Claude Bernard[3] nicotine at first produces contraction of the arteries; later on, the vessels become distended, as Rosenthal has shown in experiments on the ears of rabbits. The contraction of the vessels is followed by an increase, their distention by a decrease of the blood-pressure; Uspensky[4] concludes, from the circumstance that no increase of blood-pressure is observed after section of the spinal cord in the neck, that nicotine first stimulates and then paralyzes the vaso-motor centres. The peripheral arteries, however, are influenced independently by nicotine, as is shown by the experiments of v. Basch and Oser;[5] these authors injected nicotine into one of the arteries of the intestine, and then observed that the intestine became paler, and the seat of vascular contraction. This condition of the arteries accounts for the pallor, the cold perspiration, etc., observed in nicotine-poisoning.

The respiration, which is at first, as a rule, accelerated, after-

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[1] Allg. med. Centralzeitg. 1862. No. 103; 1863. Nos. 9 and 30; also Gesammelte Beiträge, etc. I. Bd. p. 302.

[2] Centralbl. f. d. med. Wissenschaft. 1862.

[3] Annales d'Hygiène. T. 43. See also *Oser* and *Basch*, Untersuchungen über die Wirkung des Nicotins. Wiener med. Jahrbücher. IV. Heft. 1872. p. 367 ff.

[4] Archiv f. Anat. u. Physiologie. 1868.

[5] Wiener med. Jahrbücher. 1872. p. 367 ff.

wards becomes retarded, till it ceases altogether; and this is the case even in animals, though the cause of this phenomenon is not accurately known.

Nicotine exercises a considerable effect on the central nervous system, the brain and the spinal cord. This alkaloid first acts on the brain as an excitant, and considerable cerebral excitation is produced; subsequently its excitability is reduced, so that we may rank it among the narcotic poisons. Its action on the spinal marrow resembles, on the whole, its action on the brain; it first produces excitement, and afterwards has a paralyzing influence.

The excitement of the spinal marrow is, however, but of short duration, and is rapidly replaced by diminished excitability, and this appears to occur while the brain is still in a highly excited condition. Clonic and tonic convulsions occur in cases of nicotine-poisoning both in warm- and in cold-blooded animals; these convulsions are evidently of central origin, for, according to the researches of Rosenthal and Krocker,[1] the reflex excitability of the spinal marrow is at the same time diminished. These convulsions gradually cease as paralysis of the central organ ensues; notwithstanding this condition of paralysis, the muscles still respond to irritation of their nerves. Nevertheless the peripheral extremities of the nerves are to a considerable extent sympathetically affected by the poison. These extremities, after a brief state of excitement, on which the fibrillary twitchings, so frequently observed, are dependent, become paralyzed; this can be satisfactorily shown in the frog, because in this animal there is a stage in which the muscle still responds to irritation, while it no longer contracts on stimulation of its nerve.

That the initial convulsions are not the result of disturbances in the circulation is proved by their occurring in the frog, and also by the fact established by Uspensky (loc. cit.) that these convulsions cannot be arrested by artificial respiration.

The organs composed of unstriped muscle are also affected by nicotine; for O. Nasse[2] has shown that the whole intestinal canal, but especially the small intestine, and also the uterus, may

[1] Ueber die Wirkung des Nicotins auf den thierischen Organismus. Diss. Berlin. 1868.

[2] Beiträge zur Physiologie der Darmbewegung. Leipzig. 1866.

be thrown into violent contractions by nicotine, and that these contractions may amount to actual tetanus with extreme narrowing of the lumen of the intestine. According to O. Nasse's experiments it appears that this tetanus of the intestine is due to a peripheral irritation of the intestine itself, most probably of the ganglia in its walls, for when Nasse excluded the influence of the vagus, the convulsions still occurred ; but when he arrested the circulation, the convulsions ceased ; he then injected a fluid charged with nicotine into the peripheral end of an intestinal artery, and observed convulsions to occur in the part of the intestine thus treated. These observations have been supported by similar ones by Truhart,[1] and v. Basch and Oser (loc. cit.). When these tetanic convulsions cease, either a state of repose ensues from exhaustion, or normal peristaltic movements set in, which v. Basch and Oser trace to excitement of one of the centres of intestinal movements lying in the cerebro-spinal canal, since these movements also occur when (the aorta being compressed) nicotine is injected in the direction of the brain through the carotids. A few words as to the condition of the pupil. At an early stage, and with small doses, it is usually contracted ; and dilatation occurs only under the influence of large doses of the poison. Gruenhagen's[2] view that we have only to do with an irritation of the sphincter iridis is combated by Rosenthal and Krocker, who maintain that there is simultaneous paralysis of the dilatator. Local application of the poison to the conjunctiva also caused dilatation, but (according to Gruenhagen) this was preceded by a transient contraction.

It has been a subject of dispute whether nicotine exerts a local corrosive action or not; this much is certain, that nicotine is a very powerful alkaline substance, and in a concentrated form does, in conjunction with its specific properties, produce a very painful effect on the nerves, and thus provokes reflex movements, vomiting, etc.

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[1] Ein Beitrag zur Nicotinwirkung. Dorpat. 1869.

[2] Centralbl. f. d. med. Wissensch. 1863. 577.

Results of Autopsies.

Autopsies do not furnish us with any very characteristic results in cases of nicotine-poisoning.[1] Vascular engorgements of the brain and its membranes, serous fluid in the ventricles of the brain, are mentioned in almost all published reports. The heart is generally empty, and the blood found in the vessels is of a dark-red color. The liver, spleen, and kidneys are generally hyperæmic. When tobacco has been administered internally, some remains of the tobacco may be found in the stomach and intestine ; the mucous membrane of the stomach is marked with patches of ecchymosis and erosion ; blood-stained mucus is found in the intestine, which is in a state of strong contraction.

In some cases the smell of tobacco is still perceptible in the contents of the intestine ; more frequently an odor of tobacco has been observed when the cavities of the body have been laid open ; this is scarcely ever, it is said, absent, even in experiments on animals, when dissection follows immediately after death ; other authors again, as Taylor, for instance, have failed to observe this smell.

Diagnosis and Differential Diagnosis.

The diagnosis of tobacco-poisoning is rendered difficult in some cases by the fact that the characteristic odor of tobacco too often attends other illnesses. The existence of a state of collapse in combination with vomiting and finally diarrhœa may easily lead to its being mistaken for acute intestinal catarrh, European cholera, etc. Poisoning with pure nicotine or with tobacco-juice, commencing by the patient's suddenly falling down, may be mistaken for an apoplectic attack, and the giddiness which sometimes occurs in cases of chronic poisoning may be taken for fainting.

The diagnosis is, naturally, rendered easier when any snuff or tobacco leaves have been vomited.

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[1] Reports of autopsies exist., *e. g.*, by *Dr. Skae*, Vergiftung durch Tabak. Allg. med. Centralzeitg. No. 12. 1856; by *Taylor*, Guy's Hospital Rep. III. Ser. IV. Vol. p. 345. 1859 ; and by others.

Prognosis.

The prognosis, of course, depends on the quantity of poison introduced; but since nicotine-poisoning is almost always attended with vomiting, this effort at elimination of the poison is always in favor of recovery. As a general rule, however violent may be the action of the nicotine, fatal cases of poisoning by tobacco are very rare, although serious cases of acute and chronic poisoning are frequently observed. Even very violent cases of poisoning may end in recovery, as is shown by Deutsch's case, which we have already mentioned, in which a man had taken an ounce of tobacco-juice out of a pipe, and the most violent symptoms followed, yet he recovered. The prognosis in chronic cases rests mainly on the moral energy of the patient, which may or may not enable him to renounce the use of tobacco entirely.

Treatment.

In acute tobacco-poisoning the point of primary importance is to procure the discharge of the poison as rapidly and completely as possible from the stomach and intestine. Vomiting must be encouraged as much as possible, and the stomach-pump applied, etc. Emetics themselves must be avoided, lest they should contribute to promote the collapse which the nicotine may have already determined. Enemata of vinegar, to clear out the intestine, are of much value.

Tannin[1] has been much commended as a chemical antidote; it throws down a yellow precipitate with nicotine.

When nicotine has once gained access to the blood-vessels, a more systematic course of treatment must be pursued: stimulants to promote cardiac action, cold douches, irritants to the skin, etc. In some cases of muscular rigidity and immobility, the subcutaneous injection of morphine has restored the power of movement; such a case occurred in Oppolzer's[2] clinic, in the

[1] *Lersch*, Rhein. Monatsschrift. Mai. 1851. nach dem Vorgange Henry's und Boutron's.

[2] Wiener med. Presse. No. 48. 1866.

person of a tobacco-chewer who had gone to sleep with a cigar in his mouth ; after half an hour he could not be aroused, his lips were livid, and his limbs and spine completely rigid and immovable. In grave cases every possible form of artificial respiration ought to be applied. It is scarcely necessary to say that if the poison has gained access to the body by means of open sores or excoriations, these must be cleansed by washing.

The treatment of chronic tobacco-poisoning is very simple; it simply consists in absolute abstinence from the weed.

Sometimes, but very rarely, reducing the consumption of tobacco is sufficient, but general experience shows that it is easier for the most inveterate smoker to give up smoking altogether than strictly to limit himself as to quantity; besides, relapses are much more frequent when any indulgence in the habit is permitted. Yet it is often a long time before the symptoms entirely disappear; thus, in Siebert's[1] case, four weeks' abstinence from smoking was necessary for the complete recovery of a man about thirty years of age, who suffered from deafness, a numbed sensation in his arms and hands, cardiac palpitation, double vision, paralytic symptoms, etc.

In some slighter cases it is sufficient to smoke another kind of cigars or tobacco, or to return to a kind used formerly.[2]

The amaurosis caused by tobacco-poisoning, if it is unaccompanied by any visible change in the fundus oculi, may be completely cured by the administration of strychnine.[3] Obvious anatomical changes do not disappear completely, even with total abstinence from tobacco.

Changes which Nicotine Undergoes in the Organism.

Pure nicotine is absorbed into the blood with great rapidity, circulates with that fluid, and is also very rapidly excreted, apparently in an unaltered condition. Dragendorff and Zalewsky[4]

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[1] Die Intoxication durch Nicotin. Med. Centralzeitg. No. 31. 1855.

[2] *Dr. Ritter*, Würtemberg. med. Corr.-Bl. 1–4. 1868.

[3] *P. Thilesen*, Norsk. magaz. for laegevid. XXI. p. 139. 3. Hft. 1867.

[4] Beiträge zur gerichtlichen Chemie einzelner organischer Gifte. St. Petersburg. 1872. p. 18.

succeeded in detecting nicotine (only a very small quantity, however) in the urine of a cat which expired eight minutes after the introduction of the poison into the stomach. Nicotine was found by these authors, not only in the stomach and the intestine, but also in the liver and the spleen, in the brain and in the kidneys. Taylor[1] also found nicotine in the blood as well as in the contents of the stomach of a rabbit which had been killed with one drop of nicotine.

Dragendorff and Johannson[2] proved by experiment that nicotine is also excreted through the saliva, for they distinctly detected nicotine in the saliva in the mouth half an hour after a cigar had been smoked, although the mouth had been carefully washed out with a solution of potassic permanganate. An observation by Babington[3] shows that nicotine is also found in the perspiration, for he observed that the perspiration of a man who had been poisoned by chronic tobacco-smoking smelled strongly of tobacco even after a vapor-bath.

Chemical Tests.

Stas[4] was the first who detected nicotine in the dead body. It was in the body of G. Fougnies in the cause celèbre Bocarmé. He detected nicotine in the tongue and other parts of the body, and even in the wood of the floor upon which nicotine had been spilt.

It appears from the researches of A. Melsens[5] that nicotine, as such, can be extracted from portions of the body even long after death ; he detected it in the tongues of two dogs which had been poisoned several years before by Stas. These dogs, it must be admitted, had been buried in a tightly closed barrel placed within a chest filled with earth.

[1] Treatise on Poisons. p. 662.

[2] Beiträge a. a. O. p. 18.

[3] Dubl. Journ. of Med. Science. Nov., 1866. p. 545.

[4] Recherches medico-légales sur la Nicotine. Bullet. de l'Académie de Méd. de Belgique. T. XI. No. 2. pp. 203-213. 1854.

[5] Note sur la recherche de la Nicotine dans les cadavres enfouis. Bull. de l'Academ. roy. méd. Belgique. T. XII. Nos. 9, 10. 1857-58; and Gaz. hebdomad. VI. 1. 1859.

The best method of separating nicotine from organized substances, and of testing for it, is that recommended by Stas, or we may adopt the modifications suggested by Dragendorff.[1]

First digest with water charged with sulphuric acid at 95° to 104° Fahr.; then concentrate the extract; next precipitate with alcohol, separate the alcohol by distillation, filter the watery residuum of the distillation; then shake the acid fluid with benzine in a warm place, separate the watery fluid from the benzine, make it alkaline, and take up the alkaloid with petroleum ether; this, after it has been washed with water, contains the alkaloid tolerably pure; on evaporation the odor of nicotine becomes discernible, and now the alkaloid can be tested by a series of reactions. Dragendorff[2] especially recommends testing the etherized solution of nicotine by combining with it an equal volume of etherized solution of iodine; by this means a brown amorphous precipitate is thrown down, which in a few hours forms crystals half an inch long. This reaction of nicotine was discovered by Roussin. It is specially valuable for examining any remains of the poison which may be found, and are suspected to contain nicotine.

If only small quantities of nicotine can be obtained, the so-called physiological test may be used; small birds or frogs are the best subjects for it. Frogs are seized with clonic convulsions after small doses of nicotine, and assume an attitude characteristic of nicotine poison, as van Praag and Rosenthal have shown. The thigh is placed at right angles to the body, the lower half of the leg is applied directly against the thigh, so that the feet meet together at the posterior extremity of the animal. The anterior extremities are thrown backwards and lie along the sides of the abdomen.

Poisoning with Strychnine and Plants containing it.

Strychnine ($\Theta_{21}H_{22}N_2\Theta_2$) was discovered in 1818 by Pelletier and Caventou; it crystallizes in small white tetragonal prisms,

[1] Beiträge a. a. O. p. 3.

[2] Beiträge. pp. 3, 16, 17.

terminated by tetragonal orthromboidal pyramids. It has an intensely bitter taste, and an alkaline reaction in solution. It is soluble in cold (1 : 6667) and in hot water (1 : 2500) ; it is insoluble in pure alcohol and in ether, but dissolves somewhat readily in chloroform. Strychnine, with acids, forms salts, of which the nitrate is best known ; it is used almost exclusively for physiological experiments. These salts are readily soluble in water. This alkaloid is found especially in the medicinal Nux Vomica seeds, in the bean of Saint Ignatius, in the so-called false angustura bark (bark of nux vomica), and in other strychnaceæ—the Strychnos Colubrina, snake-wood, and Strychnos Tieuté, also known under the name of Asiatic or Javanese arrow-poison, Upas radja or Upas Tieuté. O. Schulze found in this arrow-poison 60 per cent. of strychnine.[1]

Etiology.

Poisoning by strychnine may occur when strychnine, or parts of plants containing it, enter the system in any quantity. This may happen in various ways. The poison may be taken into the stomach or absorbed subcutaneously, and more readily still by the intestinal canal, as the experiments of Rossbach and Jochelsohn[2] have proved. Poisonings by strychnine are of very frequent occurrence; in England and America especially numerous cases occur every year. They are usually caused by mistaking strychnine for other substances. These poisonings occur most frequently from eating poisons intended for rats and mice, which are usually made of meal or flour, to which strychnine, and sometimes arsenic, have been added. During the last few years a whole series of such cases have been reported from England, caused by Battle's vermin-killer, or Gibson's vermin-killer, or Hunter's infallible vermin and insect destroyer. A case is reported from Hastings in which a whole family was poisoned by eating larks which had been snared with nux vomica. More frequent still are medicinal poisonings—not in Germany, but in

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[1] *Mannkopf*, Wiener med. Wochenschrift. XII. 30. 31. 1862.

[2] *Jochelsohn* in Rossbach's Pharmakolog. Untersuchungen. Bd. I. Heft 2 pp 92–114.

other countries. Apart from the circumstance that patients have sometimes taken more of medicines containing strychnine than had been ordered, many physicians have failed to take into consideration that strychnine has a decidedly cumulative action.

Again, frequent mistakes are made in chemists' shops. One case is related by B. Danvin [1] of the poisoning of a child from strychnine being given instead of santonin; another is reported by Lonsdale [2] where it was mistaken for jalapin; again, two children [3] were killed by taking strychnine instead of santonin; a child 19 months old died of [4] the same poison mistaken for tooth-powder; another was given rat-poison containing strychnine instead of rhubarb.[5] It has also been occasionally taken instead of seidlitz powder.[6] A remarkable case of auto-intoxication is reported by A. Reid,[7] of a man who prepared some mouse-poison of strychnine and meal, and introduced some of it into a slight wound in his thumb; the symptoms of poisoning were, however, very slight.

Strychnine has very frequently been used with suicidal intention, generally by doctors or apothecaries. It has also been repeatedly employed for actual murder. The most familiar case is that of Dr. Palmer, who poisoned his friend John Parsons Cook in 1855. Palmer had apparently given him repeated small doses of strychnine, till he at last died of tetanus.[8] This was followed by the case of Dove,[9] who poisoned his wife with strychnine in 1856. In 1864 Geo. F. Barker [10] published the case of a murder perpetrated by administering about 6 grains of strych-

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[1] Annal. d'hygiène publ. et de méd. leg. III. 1861.

[2] Strychnine Poisoning Monthly Journ. of Med. Feb. p. 116 et seq. 1855.

[3] Journ. de chim. med. Mai p 249. 1868

[4] Pharmaz. Journ. et Transact Juillet. 45. 1869

[5] Med Times and Gaz. 1868.

[6] Zeitschrift des allg österr. Apotheker-Vereins. No. 16. 1868. Taken from the New York Journal

[7] Med. Times and Gaz. 31. 1859

[8] For further details of this cause celèbre see Taylor on Poisons, translated by Seydeler, Die Gifte. III. pp. 316–329.

[9] Ibid. pp. 329–332.

[10] Hay's Americ. Journ. Oct. 1864. Other cases, especially from America, in Seydeler's translation of Taylor. III. Bd. p. 312 ff.

nine. Death ensued very rapidly. Lastly, we have the celebrated case of Truempy, poisoned by Demme in 1865.

As to the quantity of strychnine necessary to destroy life, about three grains seems to be sufficient. Thus, a young man [1] died from taking 3 grains of strychnine. A lady in Kensington died also of 3 grains.[2] But this figure cannot be accepted as a standard, for much smaller doses have proved fatal, and poisonings with much larger doses have ended in recovery. The German Pharmacopœia of the year 1872 states as the highest single dose of nitrate of strychnine 0.01 gramme (one-seventh of a grain), and 0.03 (not quite half a grain) per diem. Taylor mentions the death of a child from $\frac{1}{16}$ of a grain (=0.004). Husemann [3] gives as the minimum dose which destroyed life in an adult $\frac{1}{4}$ to $\frac{1}{2}$ of a grain (=0.015–0.03); cases in which $\frac{1}{2}$ to $\frac{3}{4}$ of a grain (=0.03–0.045) produced fatal consequences are reported in older and later publications. Thus Watson [4] mentions the death of a girl 13 years of age poisoned by $\frac{3}{4}$ of a grain (=0.045) of strychnine, and William Hunter [5] gives the death of a lady 70 years of age, who had taken in 42 hours, in small doses, $\frac{3}{4}$ of a grain (= 0.045), and had finally taken $\frac{1}{6}$ of a grain (= 0.01) at once. Symptoms of poisoning more or less violent set in even with very small doses; thus Leach [6] reports a case in which a grain and a third of strychnine was taken internally in 11 days, and produced violent tetanus; in a case mentioned by Pidduk [7] only one-third of a grain led to violent symptoms in an instrument-maker. Usually, however, the doses have been so large as to insure fatal results. Teinhardt [8] gives a case of a drunken apothecary, who took $\frac{1}{2}$ drachm (= 2.0) of strychnine in spirits of wine and died ; Heward [9] also mentions the suicide of a female

[1] *G. P. Wilkens.* Lancet. I. 22. May, 1857.

[2] Pharm. Journ. p. 98. 1867.

[3] Handbuch der Toxikologie. p. 508, regarding a case given by Warner in Brit. Med. Journ. Aug., 1847.

[4] Case of Poisoning by Strychnine. Monthly Journ. of Med. Science. Dec., 1845.

[5] Med. Times and Gaz. July 5, 1867.

[6] Med. Times and Gaz. Nov. 1863.

[7] Lancet. July and Aug. 1852.

[8] Cas d'empoisonnement par la strychnine. Journ. de Pharmac. et de Chimie. X. 36.

[9] Brit. Med. Journ. Sept. 18, 1869.

prisoner by 8 grains; and the suicide of a student communicated by Weyrich in Dorpat,[1] who took between four and five grains, could not fail to end fatally, from the strength of the dose.

At the same time, we have numerous cases to prove that under favorable circumstances very large doses may be recovered from. Thus Walter Chippendale[2] recovered after taking four grains (= 0.25) of strychnine; a similar case, in which Hinell[3] took nearly four grains, also ended in recovery. Th. O'Reilly[4] communicates a case of recovery after the introduction of five grains of strychnine; the largest dose yet known to have been taken without fatal consequences is mentioned by Tschepke.[5] An apothecary's apprentice took from eight to ten grains (= 0.5–0.6) of strychnine with morphine, bitter almond water, and inhalations of chloroform, and recovered. A yet more interesting case as to the quantity of strychnine taken is described by Atlee,[6] in which twenty grains of strychnine had been taken. But as in this case the poison had been swallowed directly after a meal, and as an emetic was at once administered, the recovery which ensued must be ascribed to the circumstance that the greater part of the poison was vomited.

The various parts of the plants containing strychnine have caused poisoning, nux vomica especially, just in the same manner as strychnine and its salts; nux vomica contains, according to Pelletier and Caventou, two-fifths per cent. of strychnine; an ounce or an ounce and a half therefore acts as a deadly poison, yet much smaller doses have caused death, while much larger ones have often failed to destroy life.

According to the new German Pharmacopœia the maximum dose is 0.1 gramme (one grain and a half), and 0.3 (four and a half grains) per diem. But few of these cases of poisoning by nux vomica have been recorded recently. A man[7] who had

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[1] Petersburg. Med. Zeitschr. XVI. 3. p. 125. 1869.

[2] Cases of Poisoning by Strychnia. Med. Times and Gaz. 252. 1855.

[3] Poisoning by Strychnia. Med. Times and Gaz. 252. 1855.

[4] Med. Times and Gaz. 12. 1858.

[5] Deutsche Klinik. 10. 1861.

[6] Boston Med. Journ. Dec. 15, 1870.

[7] Aerztliche Mittheilungen aus Baden. I. 1859.

taken half an ounce (= 15.0) of powdered nux vomica recovered, while another died of five drachms (20.0) after two hours, according to Pellarin.[1]

Pathology.

Symptoms and Course.

The symptoms of strychnine-poisoning are generally more characteristic than those of any other poison. They consist essentially and mainly of violent muscular contractions, which affect the most various groups of muscles, and thus may exhibit all the possible varieties and symptoms of tetanus. It is especially the extensors which are thrown into tetanic contractions by strychnine; accordingly, strychnine convulsions are characterized by the special engagement of the extensors, as is shown most strikingly in the muscles of the limbs and of the spine. The interval of time required after the introduction of the poison before the development of the symptoms varies greatly; this period of incubation depends mainly on the quantity and the form in which the alkaloid has been introduced. The most rapid case within my knowledge is that above mentioned, given by Geo. F. Barker, in which two and a half to three minutes after the introduction of about six grains (= 0.37) of the poison convulsions set in; in another case mentioned by Tracy E. Waller,[2] tetanus set in twenty minutes after four grains (= 0.25) of strychnine had been taken; in the case of a woman[3] the convulsions came on in thirty minutes after three grains (= 0.18) of strychnine; in the case of suicide described by Burow[4] convulsions did not come on till one hour after one and a half grains (= 0.19) of strychnine had been taken. Cameron[5] reports a case in which three-quarters of a grain (= 0.045) of strychnine did not produce tetanus till after one and three-quarter hours. It is self-

[1] Observation d'empoisonnement par les noix vomiques. Annal. d'hygiène publ. et de méd. leg. Oct. 1860.

[2] Philad. Med. Report. Pharm. Journ. April. 533. 1866.

[3] Journ. de Chim. médic. Mars. 125. 1868.

[4] Deutsche Klinik. 31. 1864.

[5] Med. Times and Gaz. 23. Oct. 491. 1869.

evident that the state of repletion of the stomach is an important factor in the case. In other cases longer intervals have been observed between the introduction of the poison and the first convulsion, sometimes as much as from three to eight hours. The convulsions come on in paroxysms, recurring after intervals of quiet, and so continue intermittingly till death or recovery supervenes. The duration of the intervals of rest is very unequal, and depends partly on the individual, but still more on the amount of the dose and on surrounding circumstances. In Burow's case[1] the pauses lasted only three minutes and yet recovery ensued, whereas in a case communicated by W. H. Folker[2] of a person who had been poisoned with the vermin-killer, containing about three grains (= 0.18) of strychnine, the intervals extended over half an hour, one hour, and even one and a half hours.

The duration of the paroxysms is also very unequal; they generally last longer in the case of large doses than of small, and the first attack is usually shorter than the subsequent ones; in cases which end fatally the paroxysm may last as long as five minutes, as in the case reported by Geo. F. Barker. But paroxysms of twenty minutes' duration were observed by Hemenway[3] in the case of a landed proprietor in Oregon. If the case takes a favorable turn the paroxysms diminish in frequency, the intervals become longer, and the duration of each attack is shorter. Although in general the prevailing convulsions are of a tonic character, and therefore lead to opisthotonus, trismus, etc., yet clonic convulsions are often observed in particular muscles.

The most frequent form of tetanus produced by strychnine is opisthotonus with forcible extension of the lower extremities, the head bent backwards, so that the whole body is arched; at the same time, trismus and tetanus of the pectoral and abdominal muscles occur, so that the chest and the abdomen are as hard as a board to the touch. But emprosthotonus and pleurotonus have been observed, *e. g.*, by W. Hunter,[4] though these two forms

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[1] Deutsche Klinik. 31. 1864.

[2] Lancet. July 13, 1867.

[3] Pacific Journ. N. S. Vol. I. p. 113. Aug. 1867.

[4] Med. Times and Gaz. July 5, 1867.

of tetanus are extremely rare. During the paroxysm the eyeballs are prominent and the pupils dilated; respiration is impeded in every case; the pulse is generally very feeble, and exceedingly rapid—110 to 130 beats[1] in a minute have been counted. Cyanosis, more or less pronounced, is developed, the lips become of a leaden hue, the finger-nails blue; there is also much anxiety. Even before the first tetanic paroxysm comes on, a more or less pronounced sense of anxiety and even actual dyspnœa appear; it would also seem that sometimes the glottis is early involved in the spasms—at least the convulsive screams observed in some cases would point to such a conclusion. J. Murray[2] mentions these convulsive screams in a woman poisoned by about one-half a grain (= 0.03) of strychnine. John White also observed them in the case of a maid-servant, thirty years of age, who had taken about three and a third grains of strychnine, and who was seized with complete emprosthotonus with intervals of forty-five seconds.

The convulsions give way gradually, respiration returns, the cyanosis disappears, the eye and the pupils resume their normal condition, but the frequency of the pulse continues. Consciousness remains entirely unaffected both during the paroxysms and in the intervals, unless, indeed, a high degree of carbonic acid poisoning should be set up by the paroxysms. Only one case is known to the author, in which complete unconsciousness of seventy-two hours' duration was observed, in consequence of a grain and a half of strychnine taken internally;[3] the subject, in this case, was a woman thirty-eight years of age, in whom other causes may have been at work — at least, it is very doubtful whether there was in this case a causal connection between strychnine-poisoning and the unconsciousness. While the patient is lying in bed, apparently very comfortable, with relaxed muscles and calm breathing, a fresh attack of tetanus may come on suddenly as with a blow, without the possibility of assigning any cause for it. But more commonly it comes on in consequence of some outward irritation affecting the peripheral ex-

[1] Glasgow Med. Journ. Aug. p. 488. 1871.

[2] Brit. Med. Journ. Oct. 1867.

[3] *Duriau*, Étud. clin. et méd. leg. sur l'empois. par la strychnine. Paris. 1862.

tremities of the sensory nerves, or the nerves of the organs of sense. A slight shock, a jar given to his bed, a loudly-spoken word, a flash of light suddenly introduced into the room, a brisker current of air in the neighborhood of the patient, a touch conveyed to his person, a movement on his own part, may instantly bring on a fresh paroxysm; but even if all these casualties are guarded against and avoided, the convulsions usually occur with increasing severity. After each interval, a fresh paroxysm. Much variety is observed as to the number of attacks which may occur in a case of strychnine-poisoning; some cases are reported which have terminated fatally after a few paroxysms; thus Casper [1] mentions the case of a man poisoned by from five to six grains (= 0.3–0.37) who died in the third paroxysm. In some cases, however, as many as ten have been recorded. If the poisoning terminates fatally, the patient dies either during a paroxysm with the secondary symptoms of carbonic acid poisoning, or he dies from collapse, as in the case communicated by Watson,[2] after the tetanic convulsions have ceased, while the muscles, wearied by the excessive strain, are quite exhausted and paralyzed. The first form of death, however, is by far the most frequent; respiration fails, the pulse becomes weaker and imperceptible, cyanosis becomes general, the pupils become dilated, and death supervenes.

Besides these ordinary symptoms there are occasionally others less constant. Among these are the increased secretion of saliva, sometimes observed, and vomiting. As regards the latter, it is remarkable that in most cases of strychnine-poisoning emetics fail to produce any effect, whereas sometimes, especially when strychnine has been introduced in substance, vomiting comes on spontaneously, which appears to arise from a direct action of strychnine on the mucous membrane of the stomach, upon which also small patches of inflammation are found. Harley [3] observed in a girl sixteen years of age, who had taken an indefinite quantity of strychnine, a scarlet exanthem on the inner surface of

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[1] Vierteljahrschr. für gerichtliche und öffentliche Medicin. N. F. I. 1.

[2] Monthly Journ. of Med. Science. Dec. 1845.

[3] The Lancet. II. 16. October. 1861.

the arms and legs. In Hemenway's case above quoted a remarkable form of color vision (green) was present.

The duration of the action of the poison is subject to great variation. In some cases, especially when the dose has been considerable, death rapidly ensues; thus in Hunter's case, mentioned above, the lady, seventy years of age, died five minutes after the poison had begun to act; in another case [1] death supervened in the course of fifteen minutes. In other cases death did not occur till after three hours and even more; the case reported by Weyrich, in which death was delayed for forty-five hours, was that of a student accustomed to opiates. Icterus was developed in the course of this case; it is therefore highly probable that this was not a case of pure strychnine-poisoning, but that death had supervened from cardiac paralysis, not directly traceable to strychnine. The cases which end in recovery also, as a rule, run a rapid course. When small doses have been taken recovery sets in within very few hours; but even where large doses are concerned, not many hours pass before a favorable turn takes place. After that complete recovery follows in most cases in the course of a few days. In many cases, however, the restitutio in integrum is delayed by the maintenance of certain muscular conditions.

Thus, *e. g.*, a certain stiffness of the limbs often continues for some time, accompanied with involuntary twitching and rigidity of the muscles, sometimes impeding their free play; in some cases a feeling of great weariness continues for two or three days; a convulsive shuddering in certain parts of the muscles is sometimes observed, even many hours after recovery has otherwise begun. No actual sequelæ have been noticed. In a few rare cases strongly marked muscular weakness has lingered for weeks and even months, but even in these cases it is a question whether the strychnine or the antidotes employed are the cause of the symptom; at least the case communicated by Houghton [2] justifies this conclusion. A young man had eaten a duck's egg poisoned with strychnine which had been left to poison mag-

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[1] Pharmac. Journ. p. 44. 1869.

[2] Brit. Med. Journ. June 22. p. 660. 1872.

pies. Symptoms of strychnine-poisoning were developed; he was treated with pure nicotine and a quantity of tobacco; violent headache and bleeding at the nose came on, with great prostration and muscular twitchings; he did not recover till the fourth day, and retained great weakness and tremulousness for many months.

Analysis of Symptoms—Character of the Poisoning.[1]

The tetanic convulsions which characterize poisoning by strychnine indicate, *a priori*, a change in the nerve-centres, especially in the spinal marrow, wrought by the poison. The numerous researches which have been made upon the action of strychnine in animals all agree on this point, that it is primarily the gray substance of the spinal marrow upon which strychnine acts poisonously.

The question, however, which arises is, whether the spinal marrow is itself excited by the poison, or whether it is only thrown into a condition of directly increased excitability; in other words, whether we have to do with reflex convulsions or central convulsions. Experiments on animals—especially on frogs—lead to the conclusion that the tetanus caused by strychnine is of a reflex character. After W. Arnold[2] had observed that this poison produced tetanus even in decapitated frogs, when administered in quantities so small as $\frac{1}{10000}$ of a grain (=0.00006), Professor H. Mayer[3] succeeded in establishing that tetanus failed to occur in frogs after section of the posterior roots of the nerves of the spinal marrow, or when he had paralyzed all the periphe-

[1] The principal authorities on the subject of the action of strychnine are: *Stannius*, Mueller's Archiv f. Physiolog. p. 222 ff. 1837; *Brown-Séquard*, Experimental Researches applied to Physiology. New York, 1853; *Koelliker*, Archiv f. path. Anat. v. Virch. X. 1. 1856; *Harley*, The Lancet. July 12, 1856; *Pelikan*, Beiträge zur gerichtl. Medicin. Würzburg. 1858.

[2] Experiments on the Action of Several Constituents and Preparations of Nux Vomica. Hygea. Vol. 19. 1844; and, On the Pharmacodynamic-polar Opposition of the Constituents of a Medicine. Hygea. Vol. 19. 1844. p. 390.

[3] Ueber die Natur des durch Strychnin erzeugten Tetanus. Henle u. Pfeufer's Zeitschrift für rationelle Medicin. Vol. V. p. 257.

ral cutaneous nerves. Again, the fact that a frog which has been poisoned with strychnine can be preserved from tetanus by being carefully placed under a glass bell, upon a table which stands steadily, as well as the circumstance that in the intervals of tetanic convulsions we can at pleasure arouse tetanus by touching the animal, lead to the conclusion that the tetanus is of a reflex character. To the question whether there is an exact correspondence between the case of the human subject and that of the frog and other animals submitted to experiment, it can only be answered that such is probably the case. The circumstance that human beings suffering from strychnine-poisoning often have tetanic attacks, without any previous sensory excitement, is not decisive as to the central action of the convulsions, since in strychnine-poisoning even extremely slight irritations, which under other conditions would pass unnoticed, excite tetanus, and such very slight irritations may but too easily escape observation. Since, then, it appears highly probable that in the human subject also strychnine convulsions are simply reflex, still the question arises, How is this increased reflex excitability brought about?

It is a universally acknowledged physiological fact that in frogs reflex movements occur more readily when the brain has been separated from the spinal marrow, or, as we are in the habit of putting it, when the reflex inhibitory centre is in this way removed and its action eliminated. The simple fact that tetanus occurs even in decapitated frogs, when under the influence of strychnine, proves that this paralyzing action on the reflex inhibitory centre which has been assumed is unworthy of credit. The reflex inhibitory centre, so far, at any rate, as it is seated above the medulla oblongata in the brain, is not particularly altered by strychnine. For it is a fact that persons suffering from the effects of strychnine, when they are prepared for the application of a sensible irritant, suffer no resulting paroxysm, whereas the smallest *unforeseen* irritation leads to violent tetanic convulsions. Thus numerous cases are recorded in which poisoned persons have requested their attendants to rub their skin vigorously, and this friction did not induce tetanus, whereas the kick of a foot against the bedstead produced the most violent convulsions.

On the other hand, we can conceive physiologically that there are organs in the spinal marrow also which exert a reflex inhibitory action, *e. g.*, which limit the reflex action to certain groups of muscles and prevent its extending to others, which, indeed, inhibit the communication of sensible irritations along more remote motor channels. Now the question remains unanswered to this hour whether these reflex inhibitory organs are paralyzed, or whether the excitability of the motor centres in the spinal marrow is enormously increased.

As regards the peripheral motor organs, the motor nerves and the muscles, there is no direct influence exercised on them by the poison. When an animal is poisoned with strychnine, after section of the nervus ischiadicus, the corresponding hinder extremity remains free from convulsions, although the conveyance of the poison to the extremity is not interrupted. The poison appears at the first glance to exert a directly irritating influence on the sensory nerves; but since the means we have of testing the excitability of the sensory organs is precisely the setting-in of reflex movements, and since these are already centrally influenced by the strychnine, it is clear that for the present direct experiments in this direction cannot lead to a decisive result. The condition of the vascular system is, however, decidedly influenced by strychnine. R. Richter[1] observed that in frogs and in dogs the arteries became permanently constricted during strychnine-poisoning, and the blood-pressure thereby considerably increased. S. Mayer[2] observed that after section of the spinal cord high up in the cervical region, by which means the vaso-motor centre in the medulla oblongata was isolated and rendered inert, this constriction was no longer apparent. Over and above this action on the vaso-motor centre strychnine has an influence on the heart itself. This organ is affected in opposite ways in frogs and mammalia. In frogs, during the tetanic paroxysm, the pulse is considerably retarded, especially when somewhat large quantities of the poison have been administered, and this effect may go on augmenting till the heart is arrested

[1] Zeitschrift für rationelle Medicin. (3). XVIII. 76.

[2] Wiener academ. Sitzungsberichte. Math. physic. Classe. 3. Abthlg. 1871. 9. Nov.

for a time in diastole; in rabbits and dogs, on the contrary, as in human subjects, the cardiac pulsation is usually considerably accelerated. We have scarcely any knowledge of the cause of this change in warm-blooded animals; *a priori*, we should be led to suppose that the contraction of the vascular system and the consequent increased resistance must lead to a retardation of the heart-beat, which would at the same time become stronger, and thereby contribute to an increase of the blood-pressure. It would appear from the experiments of Heinemann[1] that the vagus in its origin and course in frogs has nothing to do with the retardation of cardiac pulsation; on the contrary, this author concludes from his experiments, which showed that retardation of the pulsations did not occur in curarized animals, that it is the extremities of the vagus in the heart that are excited by strychnine, and so induce the retardation. The increase of blood-pressure in warm-blooded animals is explained without difficulty by the condition of the heart and vessels. We might be inclined to look upon the action of strychnine on the vascular system, especially the contraction of the vessels, as the primary effect of the poison, and the convulsions as secondary to this, and dependent upon it; but this view is clearly incompatible with the fact that in a decapitated frog, whose heart has been excised, tetanus can be induced by direct application of strychnine to the exposed spinal marrow, as I have convinced myself repeatedly. S. Mayer (loc. cit.) came to the conclusion that the primary effect of strychnine was on the medulla oblongata, and that the convulsions which first occur depend on its irritation, for he saw that after section of the spinal marrow high up, when the animals subjected to experiment were given strychnine, they had convulsions at first in the anterior part of their body; on the other hand, A. Freusberg[2] maintains that this distinction as to time does not exist if the spinal marrow, after section, is left for a while to recover from the mechanical

[1] Archiv f. patholog. Anatom. XXXIII. 394–414. Beiträge zur Physiologie des Herzens. I. Ueber den Einfluss der Strychninvergiftung auf die Bewegung des Froschherzens.

[2] Ueber die Wirkung des Strychnins, etc. Arch. f. experiment. Patholog. und Pharmakologie. III. Bd. pp. 204–215. 1875.

injury, and if the strychnine is not introduced till later on; in that case, he says, the spinal marrow reacts to strychnine, not otherwise, and not later than the medulla oblongata does.

In what way does strychnine kill? Formerly the answer to this question was simply—by paralysis of the spinal marrow. And even now we must admit that this is the cause of death in certain cases, viz., in those, I mean, in which death supervenes, not during a tetanic paroxysm, but by so-called collapse. If we introduce very large doses of strychnine into the body of a frog, he may die without the development of any convulsions.

We must include in the same category those cases in the human subject where death occurs after a few paroxysms. In these cases the cause of death is a sudden diminution of the excitability of the spinal marrow after a brief preceding augmentation. This diminution of the excitability of the spinal marrow may be a direct action of the poison, or it may be, as is much more probable, a lassitude, an exhaustion, which follows the initial increase of excitability.

In another series of cases of death from strychnine, arrest of respiration, from cramp of the respiratory muscles, is the cause of death. This death from asphyxia through tetanus of the respiratory muscles may supervene even when the doses administered have not been absolutely fatal, and this affords us a clue to the cause of death in cases which prove fatal after small doses of the poison. The symptoms in strychnine-poisoning seem to indicate that the brain remains intact, at least as regards its psychical function; the experiments of Alexander Ingram Spence,[1] however, show that direct application of the poison to motor centres in the brain, especially to the thalami optici, produce convulsions very rapidly; and the trismus which generally accompanies the other symptoms of poisoning can only be referred to the action of the poison on the second branch of the trigeminus at its origin.

It would be very presumptuous to hazard even a hypothetical opinion as to how the central motor centres become poisoned by strychnine. It seems to me that the working hypothesis suggest-

[1] On the Mode of Strychnine Action. Edinb. Med. Journ. July. 44. 1866.

ed by E. Gay's[1] experiments is too weak to serve our purpose. He professes to have found strychnine in the spinal marrow, in the medulla oblongata, in the pons, and especially in its gray matter; but he found most in the medulla oblongata; while he could detect none in the cerebrum. These statements need further confirmation before we can found a theory upon them. Till that time comes we must regard the action of strychnine as an example of so-called contact-action.

The results which oculists have obtained in the treatment of amaurosis with strychnine, and which they refer to the production of an increased excitability of the elements of the retina (whether directly, or indirectly through constriction of the vessels, remains undecided), throw some light on the phenomenon of colored vision, which is occasionally present.

Finally, it is evident from what we have already said that the phenomena of strychnine-poisoning are better known than those of most other poisons, and that its symptoms in the human subject may readily be recognized.

Results of Autopsies.[2]

No characteristic appearances are to be found in autopsies after poisoning by strychnine, and they furnish no positive basis for its recognition. The most striking sign is the existence of very strongly marked cadaveric rigidity. In some cases this follows so immediately upon the last tetanic paroxysm, that it may seem like a prolongation of it. In other cases, however, the muscular system is relaxed at the moment of the approach of death, and rigidity soon sets in, generally in about half an hour. It is very marked, and lasts a considerable time. In several cases

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[1] Ueber die Vertheilungsart des Strychnins im Centralnervensystem. Centralblatt für d. med. Wissenschaften. 1867. No 4. p. 49.

[2] The following are reports of autopsies: *Th. G. D. Davies*, Case of Suicidal Poisoning by Nux Vomica. The Med. Times and Gaz. Feb. 1856.—*McPherson*, Poisoning by Strychnine. Med. Times and Gaz. Dec. 1854. 233.—*Watson*, Case of Poisoning by Strychnine. Monthly Journ. of Med. Science. Dec. 1845.—*Barker*, Hay's Americ. Journ. Oct. 1864.—*Maschka*, Prager Vierteljahrschrift. Bd. 96. 19. 1867.—*Roberts*, Brit. Med. Journ. Dec. No. 34. p. 754. 1871.

it was found present even five days after death; in the Palmer case, for instance, the body of J. Parsons Cook was dissected on the sixth day after death, and the rigidity was still found complete; when the body was exhumed some two months after, for the purpose of renewed examination, the extremities were perfectly stiff and rigid.[1] The fingers are found firmly clenched, the sole of the foot arched, the ankles quite rigid. This rigidity also extends to the heart, which is usually found firm and hard, and empty of blood; yet cases are on record in which the heart was found flaccid and containing blood.

In almost all the autopsies reported the blood was found in a fluid condition.

The lungs are hyperæmic, usually with small infarctions, but these are sometimes absent; hemorrhagic erosions are occasionally found in the stomach and intestine. In a few cases fluid exudation has been found in the pericardial and pleural sacs; sometimes the urinary bladder is strongly contracted. In the abdominal glands we find the usual venous engorgement consequent on death from acute asphyxia. The condition of the brain and spinal marrow is by no means characteristic. In many of the older cases reported, marked hyperæmia of the brain was stated to have been found; but in recently reported cases, very little stress is laid on this hyperæmia. Exudations and actual hemorrhages are found in the lateral ventricles; but these are not necessarily connected with the action of strychnine. Nothing characteristic has been found in the spinal marrow. If crushed nux vomica has been taken, we find the remains of it in the stomach and intestine, notwithstanding the occurrence of vomiting. Nux vomica adheres strongly to the mucous membrane; this is partly owing to its pointed fragments, and partly to the fine hairs covering its surface, which are characteristic of nux vomica.

Diagnosis and Differential Diagnosis.

The symptoms caused by strychnine-poisoning can only be confounded with ordinary traumatic or idiopathic tetanus. But

[1] *Taylor*, Poisons, uebersetzt von Seydeler. III. Bd. p. 319.

under certain circumstances the differential diagnosis of these cases may be very difficult; in the presence of very serious wounds the decision is not difficult; but if we have only to do with slight wounds, such as the scratch of a nail, the cut of a whip, etc., and if those injuries have happened a long time ago, so that there is no history to aid us, a correct diagnosis may be very difficult. There are differences, however, between the symptoms of spontaneous or traumatic tetanus and those of tetanus caused by strychnine, which in some cases may determine the diagnosis. In the first place, in ordinary tetanus the paroxysms affect chiefly the masseters, the cervical muscles, and the muscles of the extremities, while the respiratory muscles are not so much involved; but in strychnine-poisoning, tetanus of the respiratory muscles is especially prominent. Again, the duration of each attack is generally shorter in strychnine than in ordinary tetanus; and the intervals between successive attacks are also shorter in strychnine tetanus. Lastly, in point of time the whole course in the two cases is generally quite different; strychnine tetanus usually runs its course in a few hours, whereas ordinary tetanus is generally prolonged through several days; such cases of tetanus, therefore, as are reported to last for weeks, cannot possibly be the result of strychnine. Again, in ordinary tetanus, trismus is usually the first symptom, and it frequently continues for hours, whereas in strychnine tetanus, trismus may be absent altogether, and, when present, it never lasts longer than cramp of the other muscles, nor does it ever remain the only symptom of strychnine-poisoning. It is sometimes difficult to differentiate strychnine-poisoning from apoplexy, as appears in a case given by Borchard.[1] A physician had taken sulphate of strychnine during five months, as a remedy for paraplegia, without perceiving any results from it; suddenly, at a meal, he fell over on his back, his eyes and his features became convulsed, the upper part of his arm arched, his hands clenched; there was deep stertorous breathing, the pulse was full and slow, the sensorium remained unaffected. Bleeding alleviated the symptoms, but a fresh attack shortly after terminated fatally.

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[1] Empoisonnement par le sulfat de strychnine, etc. Journ. de méd. de Bord. Juin. 355. 1855.

Absence of spasm of the gullet distinguishes the action of this poison from rabies; the preservation of consciousness prevents its being confounded with epilepsy; the nature of the convulsions, perhaps also the sex of the patient, prevents confusion with hysterical convulsions. Convulsions in hysteria are very seldom tetanic; they are mostly clonic, varying with regard to the muscles acted upon, etc.

It is more difficult to escape confounding the action of this poison with that of other poisons, *e. g.*, with picrotoxin, with certain cases of coniine-poisoning, etc. In such cases we must rely on the history or on the chemical detection of the poison in the matters vomited, or in the urine. There is one symptom which, if present, may lead us readily to a correct diagnosis, and will prevent confusion with ordinary tetanus, as well as with poisoning by other substances, and that is vomiting, as it occasionally attends strychnine-poisoning. Possibly the temperature of the body may also supply a basis for diagnosis; in ordinary tetanus this rises to 105.8° Fahr. and higher, whereas in strychnine-poisoning, especially in animals, the temperature is lowered considerably. On the whole, however, the diagnosis is not very difficult, and, indeed, few mistakes have been made, when there was an intention of avoiding them. See the Palmer trial.

Prognosis.

It has already been mentioned, in referring to the doses of this poison which have been taken in different cases, that very large doses of strychnine are not necessarily fatal, but that the result, whether death or recovery, depends on a series of incidental circumstances. If the poison is administered or taken in a form in which it is not readily absorbed, and if there is a quantity of food in the stomach, the prognosis is favorable; it is, of course, a point of fundamental importance whether vomiting occurs or not, and whether the case is taken in hand early or not. The prognosis will further depend on the length of the duration of the successive paroxysms and the length of the intervals between them. The shorter the duration of the attacks and the longer the intervals between them, the more favorable is the

prognosis, and vice versa. We must not, however, leave out of consideration the fact that many deaths from strychnine occur in intervals, from exhaustion of the spinal marrow; careful observation of the pulse and respiration will be sufficient to guard us against such a mistake as giving a favorable prognosis immediately before death supervenes. It must be regarded as a bad symptom when the pupils remain dilated during the intervals. We shall see further on, that the treatment itself is not without influence on the prognosis. How bodily conditions may promote the action of the poisoning and influence the prognosis is proved by J. St. Clair Gray's experiments,[1] which show that in frogs $\frac{1}{2000}$ of a grain (= 0.00003) is generally sufficient to produce tetanus, but when the animals were insufficiently nourished, however, and especially when their fluids were diminished by placing them on filtering paper, tetanic symptoms were produced by $\frac{1}{30000}$ of a grain (= 0.000002) of strychnine.

Treatment.

The first indication in the treatment of strychnine-poisoning is the elimination, if possible, of the poison which has been conveyed into the body. For this purpose we must give emetics, though they often fail in their action; ipecacuanha and tartarized antimony are better emetics and more certain in their action than the sulphates of copper or zinc. At the onset, the use of the stomach-pump is desirable, but later on it is apt to excite tetanic attacks, as Gaillard[2] rightly maintains. It will be well, in cases which do not permit of the use of the stomach-pump, to give simultaneously with the emetics the so-called chemical antidotes, for crystals of strychnine and pieces of nux vomica are apt to adhere so firmly to the wall of the stomach that they cannot be dislodged by the act of vomiting. Tannin and substances containing it are the best chemical antidotes. Since tannin forms with strychnine a chemical compound very difficult to dissolve, but as it is not absolutely insoluble, but is, on the con-

[1] Glasgow Med. Journ. p. 167. 1871.

[2] Bullet. de l'acad. de médic. XXIX. 19.

trary, readily soluble in acids, it is obvious that emetics should be given at the same time. According to Kurzack's[1] experiments a great excess of tannin is necessary (twenty or twenty-five parts to one). A man poisoned with a mixture of not quite four drachms of nux vomica and one drachm of indigo was seized with convulsions and was saved by emetics and a decoction of gall-nuts.[2] Alcohol, as well as acids, dissolves the compound formed by tannin, and is therefore to be avoided. What has been said of tannin is equally applicable to iodine, which should be given in the form of tincture of iodine, at first from ten to thirty drops in water every ten minutes, later on at longer intervals. Fuller[3] states that iodine throws down with strychnine an insoluble precipitate. This, however, is disputed by Darby,[4] who has proved that this precipitate dissolves when warmed as well as in the gastric juice, and that one-quarter of a grain (= 0.015) of this precipitate causes fatal convulsions in cats. Iodine may also be given in later stages of the case, if it is suspected that there is still poison in the stomach; thus B. Bennet[5] reports the case of a woman forty-two years of age, who had taken large quantities of strychnine, and on whom the iodine treatment acted very favorably. Soon after its administration the convulsions abated in violence, and after a few days she began to recover.

The administration of fat was formerly very much recommended in order to hinder the absorption of the poison. We can readily understand that when large quantities of fat are mixed with strychnine in the stomach, it retards its absorption, but it can obviously have no effect in preventing absorption in the small intestine, where fatty substances are emulsionized and saponified. It is with reason, then, that Harley[6] recommends the use of very drastic aperients together with the fat, *e. g.*, castor oil and croton oil. Some authors, on the recommendation of Morson and Garrod, have tried animal charcoal, but it has usually

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[1] Wiener Zeitschrift. N. F. III. 11. 1860.
[2] Aerztliche Mittheilungen aus Baden. I. 1859.
[3] The Lancet. April 4. p. 452. 1868.
[4] Pharmac. Journ. May. p. 435. 1868.
[5] Lancet. II. 18. Oct. 1859.
[6] Lancet. II. 16. Oct. 1861.

proved of no effect in retarding the absorption of the poison.[1] Chlorine has been credited with the property of counteracting the effects of strychnine while it remains in the stomach; this theory was first started by Dumas in 1840, and experimentally tried by Boudet,[2] who succeeded in saving sixteen out of twenty dogs whom he had poisoned with nux vomica administered by the mouth, by giving them eighty minims of chlorine water in seven and a half ounces of water, and then an emetic of tartarized antimony and a quantity of tepid water, and frequently repeating this treatment. As, however, out of the four dogs which died, there were three in whom vomiting could not be induced, it is at least very doubtful whether the action of strychnine is counteracted by chlorine, and whether vomiting is not after all the most important factor.

With regard to the treatment of particular cases, we find an immense number of antidotes recorded, of which, however, we possess but very little certain information. At the head of these stands curare, recommended by Thibaud in 1856. Vulpian[4] shortly afterwards threw doubts upron its influence as an antidote to strychnine, while Vella,[5] on the other hand, maintained that simultaneous injection of curare and strychnine produced absolutely no result, and that strychnine convulsions which have already set in cease when curare is introduced. On the other hand, Thiercelin used a compound of strychnine and curare in the form of cartridges for killing whales, and succeeded so completely with two cartridges of thirteen drachms each, that the largest whales died in from fifteen to eighteen minutes.[6] According to our present information we cannot, therefore, maintain

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[1] *Chippendale's* case, already mentioned, in which he considered that animal charcoal had wrought a cure, was not a poisoning with strychnine only, but a complete poisoning with strychnine and morphine. See Lombardia Journ. de chim. méd. Mars. 125. 1868.

[2] Sur l'emploi du chlore comme antidote de la strychnine. Revue analytique et crit'que. p. 445. 1852.

[3] L'union méd. 154, 155. 1856.

[4] L'union méd. 7. 1857.

[5] Compt. rend. T. LI. Sept. pp. 353-356. 1860.

[6] Action of Soluble Salts of Strychnine in Combination with Curare on Cetaceæ. Compt. rend. T. LXIII. 22.

that an actual antagonism exists between these two poisons. Whereas strychnine produces convulsions through its action on the spinal marrow, curare causes paralysis of the muscular system by its action on the extremities of the motor nerves in the muscles themselves. It is possible, indeed, to arrest strychnine convulsions by curare, especially by its subcutaneous injection in sufficient quantities, but there is the risk of throwing the patient into a condition of asphyxia or paralysis quite as dangerous as that produced by strychnine, only in a different way. Practically, we have almost given up the use of curare in strychnine-poisoning, because the effects of both poisons run their course side by side, and curare action ultimately gains the upper hand and causes death.[1]

Narcotics are more valuable than curare in the treatment of strychnine-poisoning.

Opium and morphine have long been used in the treatment of strychnine-poisoning, and generally with satisfactory results. Bertini[2] witnessed rapid recovery set in, in the case of a man seventy-three years of age, who had taken in two days twelve pills containing each one-fifteenth of a grain of strychnine (= 0.003), after the gradual introduction of two grains (= 0.12) of morphine acetate. A. Smith[3] confirms this, for he administered opium to a soldier who had been poisoned with two and a half grains (= 0.15) of strychnine, and recovery set in rapidly.

As opiates reduce the excitability of the spinal marrow, their use, especially in the form of subcutaneous injection, is quite rational, although we possess no histories of cases in which opiates have succeeded in arresting the effects of absolutely fatal doses of strychnine.

Chloroform is of more value than opiates in the treatment of poisoning by strychnine. The first case within my knowledge which was treated with chloroform was that reported by Mann-

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[1] *C. v. Schroff, jun.*, Wiener med. Jahrbücher. p. 420. 1872. Bericht über die im pharmacologischen Institute der Wiener Universität ausgeführten Arbeiten.

[2] Empoisonnement par la strychnine. Giornale dell' Academia r. med. chir. di Torino. Juin. 1846.

[3] Edin. Med. Journ. p. 508. Dec. 1859.

son.[1] A man forty years of age had, by mistake, taken between one and two grains (= 0.06–0.12) of strychnine; after twenty minutes complete tetanus set in; chloroform was administered for several consecutive hours, and he recovered rapidly. In a case described by Hamilton[2] four grains (= 0.25) of strychnine had been taken with suicidal purpose; narcosis, under chloroform, kept up for seven hours, resulted in recovery. Many similar cases have been reported. Chloroform narcosis has the advantage of permitting the use of the stomach-pump without danger of inducing convulsions, as Phelps has proved in a London hospital. Still, even chloroform, under certain circumstances, is unavailing in the violent effects which result from very large doses, as is shown in the case of Weyrich at Dorpat, already mentioned, in which, after from four to five grains (= 0.25–0.31) of the poison had been taken, in spite of chloroform narcosis, death supervened from cardiac paralysis. On the other hand, Copeland[3] describes a case in which five grains of strychnine had been taken (= 0.3); under chloroform the paroxysms were reduced in number and in violence, and ceased altogether after thirteen and a half hours. One pound of chloroform in all was employed on this occasion. Chloroform has been also administered *internally* in strychnine-poisoning; thus O'Farrell[4] cured a youth fifteen years of age, who had poisoned himself with two grains (= 0.12) of strychnine, by giving him, every quarter of an hour, one drachm (= 4.0) of chloroform.

The value of chloroform in the treatment of strychnine-poisoning is quite obvious. An agent which so energetically reduces the excitability of the central organs must also be capable of diminishing the over-excitability of the spinal marrow produced by strychnine, and of overcoming its consequences. Pillwax,[5] who, following in the steps of Walton and Sholes, made experiments with chloroform on strychninized dogs, found that

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[1] Inhalation de chloroforme dans un cas d'empoisonnement par la strychnine. Union méd. Mai. p. 564. 1852; and Bull. thérap. Juillet. 43. 1852.

[2] New York. Med. Record. March 1, 1867.

[3] Boston Med. and Surg. Journ. No. 6. p. 449. 1873.

[4] Philad. Med. Times. 1873. Feb. 15. p. 31.

[5] Wiener med. Wochenschrift. 6. 7. 1857.

chloroform alleviates the strychnine convulsions, shortens their duration, changes them into clonic convulsions, but does not completely counteract the effect of the poison. This we should naturally expect in the case of dogs, as they do not bear chloroform narcosis well, particularly when long protracted, and easily succumb to it. Besides, it is clear, *a priori*, that those cases in which death occurs from paralysis of the spinal marrow by very large doses are less favorable for the action of chloroform than those cases in which death is caused by asphyxia from tetanus of the respiratory muscles. It must, however, be admitted that even in these cases chloroform has a considerable palliative effect, and that it relieves patients from positive unpleasant and painful symptoms. The rapidity with which the desired chloroform narcosis can be induced, the possibility of prolonging it at will, and of renewing it *coup sur coup*, secures to chloroform the first place in the treatment of strychnine-poisoning.

Recently *hydrate of chloral*, which, since its introduction into medical practice by O. Liebreich, has become an important addition to our narcotics, has been considerably used in the treatment of strychnine-poisoning, and with much the same result as chloroform. After Liebreich himself had proved experimentally the favorable results of chloral in strychnine tetanus, Turner,[1] to the best of my knowledge, was the first to use it clinically, in the case of an Indian who had been poisoned with strychnine by his wife. He had violent opisthotonus; thirty grains (= 2.0) of hydrate of chloral were administered, with the effect of arresting the convulsions for half an hour; later on he was given fifteen grains, and then two doses of thirty grains, till at last all convulsions ceased, and he fell into a deep sleep. A milder form of medicinal poisoning, mentioned by Angus Macdonald,[2] took, very rapidly, a favorable turn, after the administration of thirty (= 2.0), and later on twenty grains (= 1.2) of hydrate of chloral. It also deserves a foremost place in the treatment of strychnine-poisoning. The experiments of Schroff, jun.,[3] proved that strychnine had no effect upon animals

[1] Philad. Med. and Surg. Rep. June 15. p. 529. 1872.

[2] Edin. Med. Journ. April. 882. 1872.

[3] Wiener med. Jahrbücher. H. 4. p. 420 ff. 1872.

poisoned with hydrate of chloral, that even deadly doses of strychnine failed to act upon an animal in this condition, but that, on the other hand, the fatal result of deadly doses of hydrate of chloral was not arrested by strychnine, so that only a one-sided antagonism exists between them.

Bromide of potassium, the main action of which is to considerably reduce the excitability of the spinal marrow, appears *a priori* qualified to act as an antidote to strychnine-poisoning. After this drug had been recommended by Th. Husemann, it was considerably employed in cases of strychnine-poisoning. A case communicated by Charles Gillespie [1] is very instructive in this respect: he treated a case of poisoning by two and a quarter grains of strychnine with a tablespoonful of a solution of bromide of potassium (1 : 3) every half hour. The paroxysms gradually gave way, and after the fifth dose the patient was able to stand and walk again. Cephas J. Bard [2] reports a case which ran an equally favorable course under treatment with bromide of potassium. Yet bromide of potassium is inferior to chloroform and chloral in rapidity and surety of action. Besides, it must be taken into consideration that bromide of potassium in such large quantities, and in so concentrated a form as is necessary for success in counteracting strychnine-poisoning, causes in rabbits, according to Schroff's observations, inflammation and ulceration of the mucous membrane of the stomach.

Atropine, the influence of which, in strychnine-poisoning, Rodolfo Rodolfi [3] tested experimentally, has, like *hyoscyamine*, no special advantages. Its effects are developed parallel, as it were, with those of strychnine, and it cannot counteract the action of strychnine except in doses sufficient to cause death. The same thing holds good with regard to *aconite*. The favorable result of Fuller's case, already mentioned, in which three grains of strychnine had been taken, is rather to be ascribed to the chloroform which was simultaneously administered than to the aconite. Besides, we must not leave out of consideration

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[1] Amer. Med. Journ. Oct. p. 470. 1870.

[2] Philad. Med. Times. June 1. p. 316. 1871.

[3] Gaz. Med. Ital. Lombard. No. 7. 1855; and Gaz. hebdomad. No. 23. 1855.

the violently poisonous action of aconite itself, which, when somewhat large doses are administered, may very easily itself prove fatal.

Recently, the *calabar bean* has been brought into notice as an antidote for strychnine-poisoning, having been recommended by Blatin.[1] Nothing conclusive can be inferred from a case in which George Ashamed[2] used it successfully on a patient poisoned with half of a grain of strychnine. Three tablespoonfuls of a solution of nine grains of calabar extract in six ounces of camphor-water were given. So far as I know, there are no other cases on record.

Cannabis indica has frequently been used as a remedy, *e. g.*, by S. A. M. Williams, in Chicago,[3] who administered the tincture, a drachm at a time, at short intervals, to a person who had been poisoned with five grains of strychnine, and was found in convulsions three and three-quarter hours after. He was cured in forty-eight hours.

Hemenway[4] also tried cannabis indica, with the addition of camphor. It seems, like opium and morphine, to be of much use, but it does not approach chloroform and hydrate of chloral in value. We find *tobacco* very frequently mentioned as an antidote to strychnine-poisoning. The effect of nicotine is to produce at first a transient increase of excitability of the spinal marrow, and this excitement is succeeded by paralysis, so that, under some circumstances, it seems possible that it may ameliorate the symptoms in cases of strychnine-poisoning. But ultimately the paralyzing effect of the nicotine will co-operate with and aggravate the paralysis which strychnine towards the close of the case induces, so that, *a priori*, the use of tobacco and nicotine cannot be strongly advised. The action of tobacco in promoting vomiting may have much to do with the success it has obtained. One of the most striking cases of the favorable effect of tobacco is that of Th. O'Reilly,[5] who poisoned himself with six grains of strychnine; then took a tablespoonful of in-

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[1] Union méd. 153. 1872.

[2] Edinb. Med. Journ. Sept. 135. 1872.

[3] Med. and Surg. Reporter of Philad.—Pharmac. Journ. July. p. 98. 1867.

[4] Pacific Journ. N. S. Vol. I. p. 113. Aug 1867.

[5] Med. Times and Gaz 12. 1858.

fusion of cigars every five minutes, and in twelve hours had perfectly recovered. The subsequent protracted exhaustion was probably due to the remedy employed. Norman Chevers[1] reports a case in which a Hindu girl who had poisoned herself with an uncertain dose of strychnine, was cured by infusion of tobacco; mention is also made in the Journal de chimie méd.[2] of a woman who, after taking three grains of strychnine, became violently convulsed; tartar emetic, bacon, and animal charcoal were tried without effect, but an infusion of tobacco brought on vomiting, and she recovered. John Meikle[3] observed a case of medicinal poisoning, in which a delicate woman, forty years of age, took a teaspoonful of nux vomica powder instead of compound licorice powder; the opistothonus which followed was subdued by the administration of enemata of tobacco (30 grs. to 8 oz. of water). Houghton's case,[4] already mentioned, shows how nicotine may influence the course of strychnine-poisoning. A young man poisoned by an unknown quantity of strychnine took two drops of nicotine in whiskey, which alleviated the convulsions, and after four drops the muscles became relaxed. The next day, the patient was ordered to smoke incessantly; he had acute pains in the head, stiffness in the neck and back, twitching of the limbs; on the third day, bleeding at the nose, great prostration and twitching of the muscles; then for some months longer great weakness and tremor. In this case it was certainly the nicotine which protracted the convalescence. Considering, then, that we possess in chloroform and chloral much better and more effectual agents, we cannot recommend nicotine and tobacco as antidotes to strychnine-poisoning.

Camphor is also amongst the antidotes most frequently used and recommended. In Pidduk's case,[5] already mentioned, a man had taken one-third of a grain of strychnine, and after taking five grains of camphor the symptoms disappeared, and did not return. Twenty grains were given in the course of eight hours.

[1] Indian Annals of Med. Science. Aug. 1. 1865.

[2] Mars. 125. 1868.

[3] Edinb. Med. Journ. Sept. p. 236. 1872.

[4] Brit. Med. Journ. June 22. p. 660. 1872.

[5] Lancet. July and Aug. 1852.

Although this case does not furnish a sufficient basis for the efficiency of camphor as an antidote to strychnine, yet it is quite conceivable that under some circumstances stimulants may be very efficacious in cases of strychnine-poisoning.

Special mention must be made of *blood-letting* and *artificial respiration* in the treatment of strychnine-poisoning.

Physicians, formerly, when they observed, in a case of poisoning by strychnine, that the patient became cyanotic, with distended and prominent veins and labored breathing, followed by a tetanic convulsion, considered that these symptoms directly indicated the necessity of bleeding. But Magendie even then called attention to the impropriety of this treatment, and it appears from Kaupp's[1] experiments, that venesection in rabbits only delays the fatal result of strychnine, but cannot avert it. The venesection, if there is still poison present in the digestive canal, necessarily induces more rapid absorption, and thus hastens the effect of the poison; besides, as the organism is weakened by the loss of blood, it is less capable of resisting the action of the strychnine, and the circumstance that, with the blood, a portion of the poison is also removed from the system, is comparatively unimportant as a set-off against this drawback. At present this remedy is very rarely resorted to.

Artificial respiration is of more value. After the statement had been made by Richter,[2] that animals under the influence of strychnine can be kept alive by means of curare in combination with artificial respiration, and when, subsequently,[3] he came to regard the latter as the chief factor in producing this favorable result, Leube[4] made experiments on hens, which led him to conclude that artificial respiration in these animals promoted recovery from strychnine-poisoning, which, however, they possess a considerable power of resisting. Uspensky[5] concluded, from fur-

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[1] Versuche über die Wirkung des Blutverlustes auf den Verlauf der Strychninvergiftung. Arch. f. phys. Heilkde. 1 Heft. p. 145. 1855.

[2] Göttingische gelehrte Anzeigen. 1862. Bd. II. p. 165.

[3] Zeitschrift f. rationelle Mediz. von Henle und Pfeufer. 3. Reihe. Bd. XVIII. 1863. p. 76 ff.

[4] Du Bois u. Reichert's Archiv f. Anat. u. Physiol. 1867. p. 629 ff.

[5] Du Bois u. Reichert's Archiv f. Anat. u. Physiol. 1868. p. 523.

ther experiments, that artificial respiration promotes recovery in brucine- and nicotine-poisoning; Ebner[1] confirmed this statement, and was of opinion that the movement of the chest in artificial respiration was the chief resisting influence against strychnine-poisoning. It appears from the experiments of Rosenthal and Leube, and Uspensky, that the *apnœa* produced by artificial respiration subdues the tetanic attacks. Hermann suggests that possibly the reflex convulsions may be suppressed by the cooling effect of artificial respiration on the animal. Rossbach failed to observe cessation of the convulsions during artificial respiration. J. Ranke states the remarkable fact that strychnine convulsions cease when a constant electric current is sent along the spinal cord, and quite as interesting is the experience of Kunde[2] that in frogs temperature influences considerably the occurrence of convulsions. When the dose of strychnine is small, the withdrawal of heat favors convulsions; when the dose is large, on the contrary, a rise of temperature promotes convulsions. Recently Rossbach and Jochelsohn[3] have examined this question, and they, with special reference to Leube's experiments, came to the conclusion that animals (their experiments were made on rabbits), according to their size and their weight, require different quantities of strychnine to destroy life, but that when absolutely fatal doses have been administered, artificial respiration can only retard the fatal event so long as it is continued, but cannot prevent it ultimately. Their view, which accords with that of Harley, refers the fatal result primarily to spinal paralysis, which is the final effect of large doses of strychnine, and secondly, to changes in the blood, which, according to Harley, is either unable to absorb oxygen in the lungs, or, after absorption, cannot assimilate it, and that it ultimately loses the power of giving out carbonic acid and absorbing oxygen; finally, they assert that death is caused by the direct reduction of muscular irritability. Rossbach's observations, moreover, go to prove that strychnine arrests

[1] Ueber die Wirkung der Apnoe bie Strychninvergiftung. Giessen. 1870.

[2] Verhandlung der phys. med. Gesellsch. zu Würzburg. VIII. 175; and Virch. Archiv. XVIII. 357.

[3] Centralblatt f. d. med. Wissenschaften. No. 24. p. 369. 1873; and *Rossbach*, Pharmacolog. Untersuchungen. Würzburg. 1. Bd. 2. Heft. pp. 92-114.

the conversion of albuminous matter into peptone, and also destroys the affinity of the latter for ozone. These effects of the action of strychnine neutralize, they maintain, any beneficial influence which artificial respiration might exert in strychnine-poisoning. Amid these conflicting statements of authors who have submitted this question to the test of experiment, it is much to be regretted that clinical observations with regard to artificial respiration are too scanty and insufficient to enable us to arrive at any definite conclusion. On the whole, we are disposed to accept as a just conclusion that which Husemann has to a certain extent adopted, viz., that artificial respiration is, after all, a rational proceeding in strychnine-poisoning, as there are cases in which death supervenes from asphyxia during the paroxysms, before paralysis of the spinal cord sets in, or when it need not necessarily set in; but, on the other hand, especially when large doses of the poison have been taken, artificial respiration is powerless to arrest spinal paralysis—all the more so because, as we shall have occasion to say further on, the elimination of strychnine from the body is not a very rapid process.

Tracheotomy has also been recommended as useful in the treatment of strychnine-poisoning; this suggestion arose out of the idea that stenosis of the glottis was the most important symptom. As we have already said, spasms of the muscles of the glottis sometimes occur, as is evidenced by the paroxysms of screaming. Poljuta[1] has made experiments as to the effect of tracheotomy in strychninized horses. Horses, into whose conjunctiva he had injected three grains (= 0.18) of strychnine in solution, were seized with convulsions in about twenty minutes and died shortly after; others which had been previously tracheotomized were injected with four grains (= 0.25), and no convulsions occurred. These results seem to show that strychnine primarily produces spasm of the glottis in horses, and that the general convulsions which follow upon these are induced by carbonic acid poisoning. But this is not the case in the human subject, therefore tracheotomy may be left out of consideration in general, especially as we pos-

[1] Ueber das Gegengift des Strychnins. Med. Zeitg. des Vereins in Preussen. No. 36. p. 178. 1854.

sess in chloroform and chloral remedies which rapidly produce relaxation of the muscles of the glottis. It is needless to add that the symptoms may sometimes indicate the application of other remedies, *e. g.*, stimulants, etc.

Changes which Strychnine Undergoes in the Organism.

Strychnine is absorbed by all the mucous membranes, even by the conjunctiva, and passes thence into the blood; similarly it is absorbed by the subcutaneous tissue; and it appears from the researches of Leube, confirmed by Jochelsohn, that it is absorbed more rapidly from the intestinal canal than from the subcutaneous tissue. It circulates in the blood, and thus reaches the different organs upon which it exerts its specific action. The next question is, What becomes of strychnine in the organism; does it leave the body again, unaltered, by the excretions or secretions? or does it undergo changes in the organism, so that it is either wholly or partially destroyed? For a long time it was supposed that the poison underwent decomposition, chiefly because attempts to detect it in the urine often failed, and the blood also yielded for the most part negative results. It was concluded that oxygen was the agent which caused its decomposition, and that the favorable action of artificial respiration might be referred to decomposition of the poison by the oxygen thus introduced into the blood; while, on the other hand, if there was a lack of oxygen in the blood, induced by tetanus of the respiratory muscles, it was believed that the poison escaped decomposition, and so worked its evil effects. All these hypotheses are now rendered groundless, as we have absolute proof that strychnine is excreted from the body unchanged in the urine. Dragendorff[1] and his pupil Masing[2] have the merit of establishing this fact. They detected the poison in the blood, though it seems to be present and detectable only in very small quantities; they also

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[1] Pharmaz Zeitschr. f. Russland. Mai. p. 320. 1867; und Beiträge zur gerichtl. Chemie einzelner organischer Gifte. St. Petersburg. 1872. pp. 185–202.

[2] Beiträge für den gerichtl.-chem. Nachweis des Strychnins und Veratrins. Diss. Dorpat. 1868.

found it in the bile, in the liver, in the kidneys, etc., but never in the brain. They found most strychnine in the liver, absolutely and relatively, whence they concluded that the poison lingered in the liver. When the poison had been taken by mouth, these authors found it long after in the stomach, and even after repeated vomiting; they also found it in the upper part of the small intestine. They never found it in the fæces, nor in the walls of the great vessels.

They did not find the poison in the urine in cases which ran a very rapid course, either because the poison is contained in too small quantities in the urine, or perhaps because, through the general vascular contraction caused by strychnine, the secretion of urine takes place more slowly than usual. Generally the excretion of strychnine in the urine appears to be a somewhat slow process. When Dragendorff and Masing introduced doses of a few milligrammes into a dog for several consecutive days, they found no strychnine in the urine till about the third or fourth day; but the excretion of the poison continued some days after the administration had ceased. This illustrates the cumulative action of the poison. The fact that strychnine was found in the bile, but not in the lower part of the intestine, leads to the conclusion that it must have been reabsorbed. Gay,[1] under Danilewski at Kasan, has proved experimentally that strychnine is also excreted through the saliva. The length of time during which the poison can be detected in the stomach may, partially at least, depend on the saliva swallowed. Dragendorff[2] has stated emphatically that in the numerous experiments he has performed "it has certainly not been proved that conditions exist in the blood which can determine the decomposition of strychnine."

Chemical and Physiological Tests.

In a case of strychnine-poisoning we should especially endeavor to recognize the poison in the matters vomited, and when

[1] Centralblatt f. d. med. Wissenschaften. No. 4. p. 49. 1867.

[2] Beiträge, etc. p. 196.

the case has been protracted, in the urine. If an autopsy is performed, the most important organs are the stomach, the liver, with the gall-bladder and bile, the kidneys, the blood, the upper part of the small intestine. Strychnine has fairly characteristic reactions. We should use for the purpose of testing—according to Otto—a solution of strychnine in concentrated cold sulphuric acid, which solution is colorless. If we introduce into this solution, conveniently placed in a small watch-glass, a crystal of potassium bichromate as large as a pin's head, and agitate the fluid by inclining the watch-glass to one side and the other, violet streaks appear, changing to blue, so that finally the whole fluid becomes violet or, with large quantities of strychnine, blue; but this color lasts only a short time; soon it passes into red, and then into a dirty-green. According to Otto, if by evaporation we obtain a residuum of strychnine on a watch-glass, we should moisten it with a solution of potassium bichromate, then quickly pour off the fluid, or absorb it with filtering-paper, and next drop some concentrated sulphuric acid on the residuum, when the blue color immediately appears. If we have enough strychnine, we may dissolve it in water charged with sulphuric acid, and add to it a solution of potassium bichromate, upon which yellow crystals of chromate of strychnine are formed, which dissolve in concentrated sulphuric acid with a blue color. A similar result is obtained by adding a small crystal of red prussiate of potash (Davy), especially if some nitric acid is added to the strychnine solution; it is also obtained by crystals of potassium hypermanganate, by potassium chromate or iodate, by hyperoxide of lead (Marchand) or manganese (J. Erdmann), etc. Otto's reaction is capable of giving positive results even with one-sixty-thousandth of a grain (= 0.000001) of strychnine, as de Vrij and von der Burg[1] have shown. Husemann's admirable work, "Die Pflanzenstoffe," gives full details of a whole series of other reactions (p. 387 ff.).

The separation of strychnine from organic substances is best accomplished by Uslar and Erdmann's method, modified by Dragendorff; the residuum, extracted by water acidulated with sul-

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[1] Annales d'Hygiène. Avril, 1857.

phuric acid and then dried, must be treated with benzine or chloroform, which fluids extract the alkaloid from the residuum, and, on evaporation, deposit it on a watch-glass, where it can then be tested according to the method given above. The microsublimation of Helwig[1] may also be used as a test; it does not, however, yield more accurate results than the chemical test. Apart from the chemical test, the physiological test may also be of some value. This consists in introducing into the body of a frog some of the residuum obtained by the process given above; if the residuum contains strychnine, the frog is seized with tetanus.

This so-called physiological test must, however, be often repeated in order to obtain an absolutely certain conclusion; care must also be taken to exclude the presence of other substances which cause tetanus, *e. g.*, picrotoxin, nitro-glycerine, brucine, and even caffeïne, which, according to Schmiedeberg,[2] produces tetanus in rana esculenta.

The fact deserves mention that strychnine resists decomposition for a long time, as appears from the experiments of Dr. Majer[3] and Riekher.[4] According to the latter, it may be detected by testing even after eleven years. Although Majer holds the test for strychnine to be one of the most certain, yet it has failed in many celebrated trials; thus in Palmer's case strychnine was sought for in vain; neither was it found in the Demme-Truempy case. This circumstance has contributed greatly in its time to confirm the hypothesis that the poison is decomposed in the body, or that it enters into combination with albuminous substances, etc.[5] The reason why strychnine cannot always be detected is due mainly to the fact that testing for it requires great and constant practice; for Dragendorff himself states, in

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[1] Das Mikroscop in der Toxikologie. Mainz. 1865. contains an atlas of photographed microscopic preparations, which show the sublimated poisons *per se*, and treated with different reagents, in their characteristic peculiarities. Dr. Erhard follows in the same direction, "Die giftigen Pflanzenalkaloide und deren Ausmittelung auf mikroscopischem Wege." Passau. 1866.

[2] Ueber die Verschiedenheit der Caffeïnwirkung an Rana temporaria und Rana esculenta. Archiv f. exp. Patholog. u. Pharmacolog. II. Bd. pp. 62–70.

[3] Würtembergisch. ärztl. Corresp.-Blatt. 25. 1857.

[4] Neue Jahrbücher f. Pharmaz. Bd. 29. 1. 1868.

[5] See *Cloëtta*. Virchow's Archiv f. path. Anat. Bd. XXXV. p. 369.

his "Beiträge," that his pupils at first were not experienced enough to detect the poison in the blood, which he himself succeeded in doing with certainty.

APPENDIX.

Poisoning with Brucine.

Brucine ($C_{23}H_{26}N_2O_4$) is constantly found accompanying strychnine in the plants which contain it, and its action, so far as is known, is completely analogous to that of strychnine, only somewhat weaker. In all cases of poisoning, therefore, by nux vomica, false angustura, etc., a part of the action is traceable to brucine. There are no instances of primary brucine-poisoning, so far as my knowledge goes.

Poisoning with Picrotoxin.

Picrotoxin is a strong poison, which is found chiefly in the Cocculus indicus; its formula is $C_{12}H_{14}O_5$; it was first discovered by Boullay in the fruit of the Anamirta cocculus; it consists of colorless, glossy, acicular crystals, generally in stellar, more rarely in foliaceous groups. It is free from odor, but has a very bitter taste; its reaction is neutral; it is soluble in 150 parts of cold and in about 25 parts of warm water; is readily soluble in warm alcohol, sparingly so in ether. It is also soluble in chloroform and amylic alcohol.

Etiology.

Poisoning by picrotoxin occurs when either picrotoxin itself in quantities of about a gramme (fifteen grains), or a corresponding quantity of Cocculus indicus is introduced into the system. Vossler [1] killed a cat in two hours by administering two grains

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[1] *v. Tschudi*, Die Kokkelskörner und das Pikrotoxin. St. Gallen. 1847.

(0.12) internally; while a dog was violently poisoned, but not fatally, by the same quantity.

Picrotoxin has been, of late years, frequently added to beer, especially in England, to increase its strength; Cocculus indicus is also used in baiting fish; it is sometimes used medicinally, and may thus lead to poisoning.

Pathology.

Symptomatology and Course.

Poisoning by picrotoxin is of rare occurrence in human beings, and we have no records of cases ending fatally.

The symptoms produced in the human subject by three grains (0.2 gramme), are nausea, vomiting, muscular debility, somnolence, and sometimes convulsions. The action of the poison on animals is better known; thus Falck's[1] researches show that fish become very restless, weak, and die from asphyxia; frogs exhibit extensor convulsions and disturbed respiration, with diminution of cardiac pulsations; in doves, in addition, there is trembling of the limbs and circular movements, with convulsions and increased flow of saliva; in cats also there is increased secretion of saliva, convulsions, and they ultimately become paralyzed; similar symptoms occur in dogs, with loud whining and scratching with the feet.

Analysis of Symptoms—Mode of Action of Picrotoxin.

To Roeber[2] belongs the chief credit of ascertaining the action of this poison. According to him, it gives rise to convulsions which, in contradistinction to those caused by strychnine, are not of a reflex nature. These convulsions assume the most various forms, and resemble compulsory movements. The pulmonary portion of the vagus is excited, hence the accelerated respiration and the strong inspiratory dilatation of the thorax; the cause of this last symptom is that the expulsion of the in-

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[1] Beiträge zur Kenntniss des Pikrotoxins. Deutsche Klinik. Nos. 47–52. 1853.

[2] Ueber die physiologische Wirkung des Pikrotoxins. Arch. f. Physiologie. p. 30. 1869.

spired air is impeded by spasm of the glottis. If the vagus is divided beforehand this symptom is absent. During the attacks reflex excitability is suspended, but it returns afterwards. Cardiac contractions are greatly retarded, the heart is very much relaxed and dilated. After destruction of the brain the symptoms are essentially the same; after destruction of the lobi optici the convulsions set in less violently; after destruction of the medulla oblongata the tetanus ceases, and we get only a comatose condition. Hence Roeber concludes that picrotoxin irritates the ganglia and the medulla oblongata, and that the motor centres, the vagus centres, and Setschenow's reflex inhibitory centre, are chiefly affected. Its influence on the heart depends partly on central irritation of the vagus, but is partly due also to excitement of the cardiac centres themselves.

Diagnosis and Differential Diagnosis.

In the case of the human subject the diagnosis rests mainly on the presence of convulsions, with accelerated respiration and retarded cardiac contraction. A superficial observer may mistake poisoning by picrotoxin with that by strychnine or brucine. This error may be avoided by knowing that sensible impressions do not lead to reflex convulsions in picrotoxin, as in strychnine-poisoning.

Prognosis.

A favorable prognosis depends on the rapidity with which vomiting sets in.

Results of Autopsies.

We find no characteristic phenomena in dissecting mammalia which have been poisoned by picrotoxin. Engorgement of the cerebral membranes and of the spinal marrow, of the plexus chorioidei, hyperæmia and œdema of the lungs, rarely pulmonary anæmia, emphysema of the lungs, hyperæmia of the liver, etc., a little clotted blood in the heart, etc., are the few positive results.

Treatment.

The first and most important step in the treatment of picrotoxin-poisoning is the elimination of the poison from the stomach by means of emetics or the stomach-pump. There are no chemical antidotes, as tannin even does not throw down any precipitate. So long as convulsions are present, narcotics—opium, morphine, hydrate of choral, even chloroform—may be administered, whereas when paralysis begins, stimulants—wine, alcohol, ether, camphor, etc.—must be employed.

Chemical and Physiological Tests.

Picrotoxino is soluble in cold concentrated sulphuric acid, yielding a golden yellow, almost saffron color, which changes into violet on the addition of a very small quantity of potassium chromate. If more of this is added the color becomes brown.

Picrotoxin mixed with three times as much nitre, and moistened with concentrated sulphuric acid, gives, on the addition of strong caustic soda to the residuum, a brick-red color. The usual procedure must be adopted for separating picrotoxino from organic substances, and it can be extracted from acid watery solutions by means of ether or amylic alcohol.

Guenkel[1] acidulates with acetic acid, adds alcohol, and extracts with ether, which on evaporation leaves a residuum of pricrotoxin in the form of feathery crystals. It reduces hydrated oxide of copper and potassium bichromate.

The physiological test depends on the action of this poison upon fish. When picrotoxin is added to the water in which they live, they make winding and boring movements of the body, alternating with quiet swimming, open their mouths and gill-covers frequently, fall on their side, and die rapidly of asphyxia.

Changes which this Poison undergoes in the Organism.

Picrotoxin passes into the blood, evidence of which, according to Vossler, is afforded by the fact that flies and fleas which

[1] Arch. der Pharmaz. CXLIV. Apr. 1858.

have sucked the blood of animals poisoned by picrotoxin, die immediately. It has not yet been proved that it is excreted unchanged in the urine, though there is a very strong probability that such is the case.

Poisoning with Coniine and Plants containing Coniine, especially Conium Maculatum.

Coniine ($C_8H_{15}N$) is an alkaloid, and in a pure condition is a clear fluid transparent as water, which evaporates at ordinary temperature; it was discovered by Giesecke as early as 1827, but Geiger was the first to prepare it pure; in late years Wertheim succeeded in preparing coniine artificially. If the alkaloid is exposed to the air, the fluid becomes at first yellow and then brown, and, finally, of a resinous consistence, while ammonia escapes. Coniine is contained in all parts of the hemlock plant (Conium maculatum), and, as Schroff[1] has shown, the alkaloid is most abundant in the seeds of plants two years old, while the leaves at the blossoming time also contain a great deal of the poison. It is sparingly soluble in water, but readily so in alcohol and ether; it has a very unpleasant odor, resembling that of tobacco-juice.

Etiology.

Poisoning by coniine was more frequent in ancient times than now. In ancient Greece, hemlock was very much used for the purpose of murder and suicide, and even for capital punishment; as every one knows, Socrates was condemned to drink the cup of hemlock, when accused of corrupting the minds of the Athenian youth and denying the gods. Cases of poisoning by hemlock do, however, occur in modern times, but they usually arise from mistaking the plant for parsley, parsnip, or chervil, or from confounding the seeds with aniseed; indeed, the two sorts of seed have been mixed together and sold. Medicinal poisonings

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[1] Wochenblatt der ärztl. Gesellschaft zu Wien.

are also on record, caused by overdoses of the poison. Bennet [1] reports a case in which a man, forty-three years of age, died of poisoning, caused by mistaking this plant for some other vegetable. Attilio Bianchi [2] describes the poisoning of two children, seven and eight years of age, by eating hemlock-root. A case of murder by this poison also occurred recently. In the year 1861, Dr. H. Jahn, of Dessau, poisoned his mistress, L. B., with coniine. It has been asserted that many animals, *e. g.*, birds, goats, sheep, and even cows, enjoy immunity from the action of the conium plant, while human beings may be poisoned by eating the flesh of these animals. This immunity, however, is not yet satisfactorily proved. A case of suicide [3] by Conium maculatum committed by an American, Dr. Walker, at New York, in the summer of 1875, was reported in most of the German newspapers. It is impossible to state with accuracy what constitutes a fatal dose of this alkaloid or of the parts of the plant containing it. The new German Pharmacopœia prescribes 0.001 ($\frac{1}{65}$ of a grain) per dose, and 0.003 ($\frac{1}{22}$ of a grain) per day, as the maximum dose of coniine, of hemlock leaves 0.3 (four and a half grains) per dose, and 2.0 (thirty grains) per day. So that coniine is among the most energetic poisons with which we are acquainted.

Pathology.

Symptoms and Course.

When coniine or conium is taken, it creates a burning sensation in mouth and throat, and pain in the tonsils, as Schneller [4] found by trying small doses on himself. Neligan [5] observed also constriction of the gullet and difficulty of swallowing in a pro-

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[1] Empoisonnement par la cigué. Journ. de Phys. et de Chimie. T. X. p. 123. 1846.

[2] Gaz. Lombard. 21. 1857.

[3] This case should not be described as "suicide." A preparation of hemlock was prescribed medicinally, and the patient, a great sufferer, took dose after dose in violation of the careful instructions of the prescriber, probably in the vain hope of obtaining the relief which the doses as ordered failed to procure.—E. C.

[4] Pharmacologische Studien. Zeitschr. der Wiener Aerzte. März. 1846.

[5] De l'emploi de la cigué dans les effets douloureuses. Jour. de Phys. et de Chim T. IX. p. 119. 1846.

tracted case. Increased flow of saliva has been observed[1] by Schneller and Flechner.

If coniine has entered the blood in sufficient quantity, the poisonous effect sets in early and with tolerable rapidity. In many cases the poisoned persons fall down suddenly ; soon after this, a marked degree of muscular debility sets in, with dyspnœa and marked præcordial distress. The respiratory movements become labored and slow ; the pulse is also considerably retarded, and paralysis of the voluntary muscles follows. The respirations become slower and slower, till after some time they cease altogether, generally in a few minutes or hours, while the cardiac action continues. Consciousness usually remains intact ; at the utmost a swimming in the head sets in ; thus it is explicable how Socrates could continue his conversation with his friends up to the moment of death. The pupils are constantly dilated, and disturbances of vision are common. In many cases vomiting ensues, and towards the close of the case clonic convulsions set in, which are apparently traceable, partially at least, to the accumulation of carbonic acid in the blood in consequence of impeded respiration. In the case of the two children whose poisoning Bianchi describes, the facial muscles were strongly implicated in these convulsions, as well as the extensors of the spine and the flexors of the limbs. If these symptoms continue, the temperature of the body becomes much reduced ; the skin becomes pale, and death ensues. If the case takes a favorable turn, the respirations become more frequent, the highly-marked cyanosis diminishes, and the normal condition is gradually restored ; but recovery is very slow, and an intense muscular debility remains behind, which manifests itself chiefly by tremor of the legs.

Analysis of Symptoms—Mode of Action of Coniine-Poisoning.

The most striking feature in the action of coniine is the muscular paralysis it induces, which ultimately extends to the respiratory muscles, so that breathing becomes impossible. This muscular paralysis is due to the influence of coniine on the peri-

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[1] Beiträge zur Physiologie der Arzneiwirkungen. II. Zeitschrift der Wiener Aerzte. Juni. 1847.

pheral extremities of the motor nerves, as well as on the motor centres. For when Albers[1] injected coniine subcutaneously into a frog's leg, it was very soon completely paralyzed, and shortly after the paralysis spread over the whole body. Koelliker,[2] who has earned so much distinction by his researches into the physiological action of so many poisons, proved that it is the extremities of the motor nerves in the muscles which are paralyzed by coniine in the first instance; the muscles themselves as such remain excitable, unless the poison is directly applied to them, and then, as it excites a local corrosive action, it destroys their power of contracting. It appears from the researches of Damourette and Pelvet,[3] and of Verigo[4] that, besides the peripheral action of coniine, it also acts upon the motor centres. According to Guttmann,[5] whose statement is entirely confirmed by the researches of Koelliker and Ihmsen,[6] the trunks of the nerves are also paralyzed, but at a very late period. The sensory nerves are affected by coniine, though only in a subordinate degree; this fact is observed and established less by physiological researches than by actual experience in the case of human beings. Thus Guttmann asserts that coniine, applied to the cuticle, renders it anæsthetic; this is confirmed by the fact that the hands of people who express hemlock become completely insensitive. Even in ancient times priests[7] were recommended to use friction of the hemlock plant in the region of the genitals to enable them the more easily to keep their vows of chastity and continence. The statements of therapeuticians that coniine alleviates the reflex spasm in photophobia,[8] and produces a general anæsthetic effect, is consistent with the foregoing.[9]

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[1] Ueber die Wirkung des Theins auf das Herz u. die physiol. Wirkungen des Coniins. Deutsche Klinik. No. 34. 1853.

[2] Physiologische Untersuchungen über die Wirkung einiger Gifte. Virch. Arch. Bd. X. p. 235 ff. 1856.

[3] Gaz. méd. de Paris. 1870. Nos. 9–37; and Bull. de Thérap. 1870. Juin–Decbre.

[4] Deutsche Zeitschrift für Staatsarzneikunde. XXVIII. 213.

[5] Ueber Coniin. Berlin. klin. Wochenschr. Nos. 5, 6, 7, 8. 1866.

[6] Disquisitiones physiologo-toxicologicæ de Coniino. Dissert. Petersburg. 1857.

[7] *Doellinger*, Heidenthum und Judenthum. p. 171.

[8] *Spengler*, Ueber die Wirkung des Coniin. Neue Zeitsch. für Med. u. Med. Ref. Bd. I. Hft. 1. 1850.

[9] See *Neligan*, l. c.; *Reuling* and *Salzer*, Ueber die Wirkung des Coniins. Deutsche Klinik. No. 41. 1853.

Death is sometimes preceded by convulsions ; in frogs they are always absent, in mammalia they are almost constant. These convulsions might be regarded as simple consequences of carbonic acid poisoning, and certainly a number of them depend on respiratory disturbances ; but Guttmann's experiments make it very probable that these convulsions may be directly caused by the central action of the coniine, as he failed to arrest by artificial respiration the convulsions produced by coniine.

The respiratory disturbances, which consist in a remarkable retardation of the respiration, are only the consequence of the action of coniine on the nerves of the muscles. The action of the heart is also affected by this poison, though much more slightly, and it continues to beat to the last. As a general rule, cardiac pulsation is retarded in coniine-poisoning. It would appear from Boehm's[1] investigations that the cardiac extremities of the vagus are paralyzed by coniine, but not the actual inhibitory centres, the excitability of which remains unaltered. The fall of temperature in animals poisoned by coniine depends partly on the action of the poison on the vessels which, according to Guttmann, are dilated. Nega[2] also speaks of diminished innervation of the vessels caused by coniine. According to the views of Leonidas van Praag[3] and Danilewsky[4] this poison exerts a primary action upon the brain and spinal marrow. v. Praag attributes death by coniine to paralysis of the spinal marrow. Danilewsky speaks of an initial excitement followed later on by paralysis of the hemispheres and of the reflex apparatus. Thus respiratory paralysis is to be regarded as the main effect of coniine ; this paralysis itself depending on the paralysis of the intramuscular extremities of the motor nerves ; death by coniine is therefore caused by its action on the respiratory organs.

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[1] Studien über Herzgifte. p. 88. 1871.

[2] Das Coniin als Arzneimittel. Günsburg's Zeitschr. f. klin. Medic. Bd. I. Hft. 1. 1850.

[3] Coniin, Reil's Journal f. Pharmacodynamik, Toxikologie und Therapie. I Hft. p. 1 ff. 1856.

[4] Arch. f. Anat. u. Physiol. Hft. 6. 1866.

Diagnosis and Differential Diagnosis.

Coniine-poisoning may be recognized by the consequent adynamia, followed by loss of muscular power, together with dyspnœa, while the cardiac contractions remain comparatively unaffected. The action of this poison has the greatest resemblance to that of curare, only the paralytic symptoms in curare are much more pronounced, while in coniine they are not so fully developed, at least in mammalia. If convulsions come on before death the diagnosis of coniine-poisoning is much more certain; also it may help us if we remember that Conium maculatum grows wild with us, whereas curare is very difficult to procure. The acuteness of the attack, and the fact that all the muscles are equally involved in the paralysis which it occasions, may help us to distinguish this form of poisoning from ordinary diseases of the spinal marrow. The diagnosis may, of course, be aided by the inspection and examination of the vomited matters, since we may find there the remains of parts of the plants which have been eaten, and recognize them by their appearance and odor.

Prognosis.

The prognosis in coniine-poisoning is necessarily, in the first instance, dependent on the quantity of the poison in operation; vomiting at an early stage is favorable; practically the condition of the respiration is of the greatest importance; the less it is impeded the more encouraging the prognosis, and vice versa.

Results of Autopsies.

When we do not find portions of plants in the stomach which can be certainly recognized as conium (the best test is to develop the unpleasant tobacco-like odor of coniine by reducing the leaves to powder with caustic potash), there are no really characteristic phenomena in autopsies after death by this poison. The blood is generally found in a fluid condition, and appears to resist coagulation; it is red, and becomes redder when exposed

to the air. Hyperæmia of the brain, and especially of its meninges, is said generally to exist. In the lungs, as well as in the great abdominal glands, we find the signs of death from asphyxia, venous hyperæmia, and œdema. When pure coniine has been administered, some redness, etc., is found in the stomach, but when the leaves of the plant have been eaten, green mucus is generally the only thing to be found there.

Treatment.

The first point in the treatment of coniine-poisoning is to eliminate the poison as rapidly as possible by the use of emetics or the stomach-pump. The second is the application of stimulants to the spine to promote respiratory action. Respiratory movements must above all things be kept up, and therefore artificial respiration must in some way or other be maintained. The best therapeutic result may be expected from this, as the action of the heart is comparatively so little affected. Tannin is to be recommended as a so-called chemical antidote; it forms a precipitate with coniine.

Changes which Coniine undergoes in the System.

Coniine passes unchanged into the circulation; absorption takes place with tolerable rapidity from the mucous membrane of the stomach and intestine. It is not decomposed in the organism, for it can easily be detected unaltered in the blood, the liver, and the urine, by which it is excreted. The elimination of the unchanged poison in the urine occurs with considerable rapidity, for coniine was found in the urine shortly after its administration by Paul Zalewsky[1] who, under the direction of Dragendorff, experimented on the detection of coniine in the organism.

Chemical Test.

The tests given for coniine are by no means characteristic of this poison only. The following process is that given by Dra-

[1] Untersuchungen über das Coniin in forenser Beziehung. Dorpat. 1869.

gendorff and Zalewsky after many experiments in detecting coniine in organic substances:

Reduce the substances to powder, dilute them if necessary, and digest with dilute sulphuric acid (one part to five parts of water) for twenty-four hours, at a temperature of from 95° to 140° Fahr., filter, concentrate the filtrated substance, mix it with three or four times its volume of alcohol, leave it twenty-four hours, and filter. The alcohol is separated from the filtrate by distillation (in a water-bath).

After it becomes cold, filter again, shake the filtrate twice with half its volume of benzol, mix with ammonia, shake with one-quarter its volume of petroleum ether, and finally wash with water. The petroleum ether, on evaporation, leaves the alkaloid behind. This is recognized as coniine, first, by the odor, which, however, may be deceptive or disappear; secondly, and chiefly, by the characteristic crystalline form of coniine hydrochlorate.

Pour a few drops of hydrochloric acid on a watch-glass, and add a few cubic centimetres of the petroleum ether extract, and evaporate the mass at from 68° to 86° Fahr.; the residuum is a delicate iridescent film, which, when magnified 100 times, is seen to consist of acicular crystals, hanging together by lateral offshoots, and mingled with numerous small granular bodies. The crystals produce double refraction of light (Helwig[1] has given drawings of these crystals), and have the odor of coniine, which is rendered more intense by breathing upon them. The solution of these crystals in dilute sulphuric acid throws down with potassium-bismuthic iodide an orange-colored precipitate, which is discernible even when diluted one-six-thousandth times. It also throws down a precipitate with molybdo-phosphoric acid.

Poisoning with Cytisine and Plants containing it.

Cytisus Laburnum.

Cytisine ($\Theta_{20}H_{27}N_3\Theta$) is the alkaloid which was discovered by A. Husemann and Marmé, in 1864, in various parts of the Cyti-

[1] Das Mikroscop in der Toxikologie.

sus Laburnum ; it is also found in several other species of Cytisus. It appears as a white, glistening, crystalline substance, which is devoid of odor, but has a bitter and slightly caustic taste ;[1] it has an alkaline reaction, is readily soluble in water and alcohol, but is not soluble in ether or chloroform.

Etiology.

A considerable number of cases of poisoning by the Cytisus Laburnum have been published. Christison[2] relates the poisoning of a cook, into whose soup a man-servant had thrown a piece of the bark. Sedgwick[3] saw two children who were poisoned by chewing the root of the shrub instead of licorice root. Lesage Picon[4] saw six persons of one family made ill by eating laburnum blossoms instead of baked acacia blossoms. The seeds of the laburnum are also poisonous, as is proved by the observation of John Popham,[5] who saw ten boys who had been made ill by eating them. George Fischer[6] relates that two children, two and a half and four and a half years of age, ate some pods of Cytisus Laburnum, and became violently sick. Wilson[7] mentions the death of a child who had gnawed at laburnum bark ; the case terminated fatally in eight hours. Dr. Rouge[8] communicates a case in which a company of fourteen persons were poisoned by eating cakes which had been made with laburnum blossoms instead of acacia blossoms. Graham[9] mentions a case in which sixteen girls, from two to nine years of age, had eaten laburnum seeds. Weelhouse[10] reports a second case of death : a young girl five and a half years of age ate unripe pods of laburnum, and

[1] *Husemann* und *Marmé*, Zeitschr. f. Chem. 1865. 161.

[2] Poisoning with the Bark of Cytisus Laburnum. London Med. Gaz. Oct. 1843.

[3] Med. Times and Gaz. Jan. 3, 1857.

[4] Rev. thérap. du Midi. XIII. p. 396. 1859.

[5] Dubl. Med. Journ. Feb. p. 248. 1863.

[6] Schuchardt's Zeitschr. für prakt. Heilkunde. Hft. 5. p. 408. 1867.

[7] Lancet. Jan. 18. p. 86. 1869 ; and Pharm. Journ. Feb. 1868. p. 395.

[8] Revue méd. Tom. 1. 15. Feb. 1868. p. 191.

[9] Med. Press and Circul. July 29, 1868.

[10] Laburnum-poisoning. Brit. Med. Journ. Jan. 22. p. 79. 1870.

died in nine days of the poisoning. Henry Wilson[1] gives a case to prove that even a small number of seeds may produce cytisine-poisoning: a boy four years of age became violently sick after eating ten seeds. The latest reports of cases ending in death were communicated by Hinkeldeyn:[2] three children at Lübeck had eaten pods and seeds of laburnum; two children, each five years of age, fell into convulsions, were seized with violent vomiting, the matters vomited being mixed with blood, and died in a very short time. A case of medicinal poisoning by a decoction of cytisus blossoms is reported by Pollak,[3] in which a girl at Teheran suffering from dropsy, after taking the decoction, was seized with vomiting and diarrhœa, with violent collapse.

No cases of poisoning with pure cytisine or its salts have been hitherto observed; it is therefore impossible to state accurately what quantities produce poisonous effects. According to Marmé's investigations, about half a grain (0.03–0.04) is sufficient to kill cats by subcutaneous injection; when injected into the blood, from one-sixth to one-fourth of a grain (0.01–0.015) killed large rabbits and cats; half a grain (0.03) destroyed life in dogs.

Symptoms and Course.

As a rule, symptoms of poisoning set in very soon after the poisonous constituents of plants have been taken; the nausea and vomiting which precede the other symptoms set in in some cases in a few minutes, whereas in other cases hours may elapse before these symptoms appear; this circumstance most probably depends upon the repletion or emptiness of the stomach. Among the first symptoms are generally headache, giddiness, swimming in the head. Afterwards we often get dryness of the throat, a sensation of heat in the head, and a feeling of great general debility. These symptoms may last a longer or shorter time; vomiting has sometimes been observed to continue twenty-four hours (Christison).

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[1] Lancet. Sept. 16. p. 391. 1871.
[2] Deutsche klinik. 27. p. 252. 1873.
[3] Wien. med. Presse. 9. 1868.

Another symptom in most cases is diarrhœa, sometimes of a very persistent character. The vomiting and diarrhœa are generally attended by violent pains in the stomach and intestine. In slighter cases of poisoning, in addition to these symptoms, collapse may also be induced, due in part to the acute drain of fluid. In severe cases motorial disturbances occur, convulsive twitchings in the face and limbs, complete incapability of walking, cramps in the muscles of the eyes, etc. The heart-stroke is generally accelerated, and is weaker than in the natural condition; the respiration is labored and difficult, the temperature reduced; the patient has an anxious expression; the pupils are generally dilated; there is great thirst and great restlessness. This jactitation is followed in some cases by a condition of sopor with loss of consciousness, which, however, may return for a while. Death supervenes with the symptoms of asphyxia, either with or without convulsions, and is preceded generally by loss of consciousness (Hinkeldeyn's case). In Weelhouse's case death did not supervene till the ninth day after the poisoning, the prostration caused by the vomiting and the persistent dysenteric diarrhœa leading finally to a fatal result. In the one case mentioned by Hinkeldeyn death occurred through rupture of the stomach in consequence of the vomiting. In a few cases actual hallucinations and delirium have been observed; very many cases are attended with sleeplessness. The debility and this sleeplessness may under some circumstances last a long time; for instance, it lasted for a whole week in the case of a girl, eighteen years of age, communicated by Tinley[1]; in Christison's case of the cook who was poisoned, the debility and alternate vomiting and diarrhœa lasted more than six weeks, so that she was obliged to give up her place, and recovered very slowly. But in general convalescence sets in early, and the health is restored to its usual condition in a few hours or days.

Analysis of Symptoms—Mode of Action of the Poison.

By Christison's suggestion, Dr. Ross, more than thirty years ago, made experiments with Cytisus Laburnum, which showed

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[1] On a Case of Poisoning by Laburnum. Lancet. Aug. 6, 1870.

that it caused vomiting and diarrhœa in dogs and cats, but in rabbits it caused convulsions, often amounting to tetanus. We are indebted to W. Marmé[1] for a thorough examination of the effects of cytisine. This investigator made experiments on all kinds of animals with nitrate of cytisine, and proved by experiment that the poison might be absorbed from all possible points of application. As to the effect of cytisine, he observed chiefly two stages, distinct from one another, that of jactitation and that of depression. At the outset of the case he often observed symptoms of tetanus; the spinal marrow and the motor nerves are at first excited, later on paralyzed, and the paralysis begins in the peripheral extremities of the motor nerves. The muscles are also affected, but much more slightly than their nerves; in this way the disturbances observed in the motor apparatus in human beings are accounted for. The respiration is at first accelerated, then retarded and dyspnœic; cardiac contraction is accelerated by stimulation of the excito-motor ganglia; the peristaltic contraction of the intestine is increased, hence the diarrhœa. Consciousness seems to remain intact in animals.

Results of Autopsies.

There are very few published reports of autopsies after cytisine-poisoning, and the few which are known contain nothing characteristic of this poison. We should expect from the symptoms observed in life to find evidence of gastro-enteritis in the intestinal canal. Hinkeldeyn, however, who performed two such autopsies, expressly states that he found no trace of inflammation in the stomach and intestine. In one case this author found perforation of the stomach, as the result of violent vomiting when the stomach was replete.

Diagnosis and Differential Diagnosis.

The diagnosis of cytisine-poisoning must rest in the first place upon the history of the case, and then upon the examina-

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[1] Ueber Wirkung u. Vorkommen des Cytisins. Nachrichten der Göttinger Societät der Wissenschaften. p. 24. 1871.

tion of the vomited matters, which may contain portions of the parts of plants which have been eaten. If these data are absent, it will be very difficult to diagnose the poisoning with certainty, as all the symptoms which are produced by cytisine belong more or less to other poisons, and specially also to emetics. It is possible to mistake its action for that of a so-called drastic emetic, or with acute gastro-intestinal catarrh, or even with arsenical poisoning or cholera. It is worthy of note that poisonings with Cytisus Laburnum occur almost exclusively in summer, when the tree is in blossom, and that in general only children and thoughtless young persons are poisoned by it.

Prognosis.

From what has been said, it follows that death very rarely occurs from cytisine-poisoning, so that the prognosis is generally favorable. This is due to the spontaneous vomiting, by which the greater part of the poisonous matter can be eliminated from the body before absorption. The prognosis will be all the more favorable if but a small quantity of the poison has been swallowed, if vomiting sets in rapidly, and if there is not much gastric disturbance or collapse. It is also of consequence that a rational treatment should be adopted as soon as possible.

Treatment.

In the treatment of cytisine-poisoning we must begin by administering an emetic, etc., so as to procure the elimination of the portions of the plant which have been introduced. So-called chemical antidotes are not of any special value here. Tannin, *a priori*, might have been thought of use, but, though it throws down a precipitate with cytisine, it dissolves it again when added in excess (Marmé). At a later stage of the case stimulants are indicated to avert threatened collapse. Opiates may also act favorably in relieving the jactitation and colicky pains and hypercatarrhsis. In severe cases, artificial respiration should be had recourse to, for Marmé found that animals which had been

poisoned with deadly doses of cytisine could be kept alive by artificial respiration.

Changes which Cytisine undergoes in the Organism.

All that we know about the changes which cytisine undergoes is due to the researches of Marmé. Cytisine passes unchanged into the blood, and is excreted again unchanged through the urine, in which it can be detected both chemically and by physiological experiment.

The chemical test of cytisine, its extraction from organic substances, etc., have never yet been asked for in evidence.

APPENDIX.

Poisoning with Cicuta Virosa, Œnanthe Crocata, Æthusa Cynapium.

Poisoning with the different parts of the water-hemlock (Cicuta virosa), is tolerably frequent and very dangerous, especially when the root and seeds are in question. Dr. Meyer[1] speaks of four children from three to six years of age, who were violently poisoned by eating the roots, which they mistook for turnips. The youngest child died the very same day with pains in the bowels, vomiting, and convulsions in different groups of muscles. The three others had violent pains in the bowels, giddiness, loss of consciousness, and general convulsions, but recovered by the use of emetics, tannin, and cutaneous irritation. Schlesier[2] also observed a very severe case in a child eight years of age, who was found lying unconscious and insensible, with feeble, stertorous respiration, and dilated pupils, the abdomen distended, and meteorism strongly marked. The child was restored to consciousness by bleeding, cutaneous irritation, and stimulants; he recovered the power of voluntary movements, the breathing became calm and regular, only incapability of swallow-

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[1] Med. Zeitg. f. Preussen. No. 40. 1842.

[2] Zur Lehre von der narkotischen Vergiftung. Kasper's Wochenschrift. No. 7. 1848.

ing remained. In spite of this improvement death from collapse supervened the following night. Many similar cases of poisoning, but generally of a slighter kind, are recorded.

The active principle, cicutine, has never yet been isolated in a state of purity, and no experimental investigations have been made into its mode of action. The treatment likely to be most effectual is the use of emetics and laxatives, liquids containing tannin, coffee, etc., also stimulants, camphor, ether,[1] etc.

Œnanthe crocata has also frequently led to poisoning. Thus Dr. Nicol[2] mentions that a woman who was suffering from a skin disease took a decoction of the roots of this plant; very soon loss of power set in, with vomiting and diarrhœa, then convulsions came on, and death supervened an hour after the decoction had been swallowed. Smiley Kane[3] has related a case of a little girl, four years of age, who mistook this root for parsnips; vomiting first set in, and then a peculiar rigidity of the whole body, trismus, twitchings of the face and the muscles of the fingers, very labored respiration. Recovery was induced by the use of chloroform inhalations, enemata of turpentine, and stimulants. Bloc[4] collected 124 reported cases of poisoning by Œnanthe crocata, five of which ended fatally. The root of this plant contains a yellow juice which has a very powerful irritant action, excites coughing, and produces inflammation of the skin like that caused by the nettle. What we find described under the name of œnanthine and œnanthine resin is not a pure substance, but contains the poisonous principle of Œnanthe crocata.

The treatment of poisoning by Œnanthe crocata must be almost identical with that of poisoning by Cicuta virosa.

Symptoms of the same kind are produced by the roots of Æthusa Cynapium, which, according to Ficinus,[5] contains an alkaloid, cynapine. Evan Thomas[6] observed three cases of poi-

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[1] See *Maly*, Vergiftung mit Wasserschierling. Oesterr. med. Wochenschrift. Sept. 1844.

[2] Case of Poisoning by Œnanthe Crocata. Assoc. Med. Journ. March 10. pp. 224 and 233. 1854.

[3] Med. Times and Gaz. Sept. 25, 1869.

[4] Montpellier méd. 1872. Oct., Nov., Dec.; and 1873. Mars, Avril.

[5] *Husemann*, Pflanzenstoffe. p. 280.

[6] Cases of Poisoning by Æthusa Cynapium. Med. Times. Aug. 1845.

soning in children, one of whom died, but the others recovered. All had very violent pains in the stomach and intestine, very violent vomiting, and difficulty of swallowing. In medical literature, a series of this and similar poisonings are on record; thus, in 1869, five members of one family became ill from eating a veal-pie which had been flavored with fool's parsley instead of ordinary parsley (Chevallier). All recovered under judicious treatment, although violent gastric and paralytic symptoms had set in.

Evidences of gastro-enteritis are generally found in the bodies of persons poisoned by Æthusa Cynapium. We have no experimental evidence as to the action of this poison, and treatment must be that which has been recommended for the other poisonings just mentioned.

Poisoning by Curarine.

Curare.

Poisoning by curare is from a practical point of view of very subordinate importance for us, as far as the probability of its occurrence within the range of our own experience is concerned. But this poison has a very strong theoretical interest from a physiological and toxicological stand-point. This, as well as the circumstance that curare is employed as a medicine, and has sometimes, though rarely, induced poisoning, may justify our giving it a place here.

Curarine is the active principle of a series of poisons which are indigenous chiefly in South America, and which have been prepared by the different tribes of Indians, sometimes from different plants, and sometimes mixed up with a number of various ingredients of doubtful nature. It has received the various names of Wurali, Urari, Macusi Urari, Ticunas, and others. The different kinds of curare are obtained from different plants, and these are only imperfectly known. Thus Strychnos toxifera, Strychnos cogens, Paullinia cururu, etc., yield this poison. Some

kinds contain mixtures of snake-poison or toad-poison, or other substances which are innocuous, so that the various kinds differ in their poisonous properties. W. Preyer was the first to procure curarine in a crystalline form from curare, and he asserts that this alkaloid acts twenty times more powerfully than curare; according to others, the difference is not so marked; thus, Beigel[1] states that it is only six times stronger than curare; these conflicting opinions are easily explained by the difference in the original preparation of curare by the Indians.

Etiology.

The Indians on the Orinoco, on the Amazon, etc., use curare for poisoning the points of their arrows, with which they hunt animals as well as attack their enemies. Many a European may have been killed in this way. Thus Ferreira de Lemos[2] mentions an attack made by the Indians upon the members of a boundary commission. One man received three wounds and died in three hours; others who at once washed their wounds with salt water, were not ill at all, while the secretary of the company, wounded by three arrows, at first showed slight symptoms of curare-poisoning, but remained ill for months simply in consequence of the wound as such. W. Preyer[3] induced slight curare-poisoning in himself, from some of the powder making its way into his body, while he was pulverizing it for his scientific investigations. He also reports a slight case of poisoning which occurred to a man twenty-three years of age, who by chance had admitted a few drops of solution of curare into a cut. Lastly, cases might be mentioned, which have arisen out of the intentional medicinal clinical use of curare, but which, so far as my knowledge goes, have never ended fatally.

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[1] Berlin. klin. Wochenschrift. 7. 9. 33. 1868; and Journ. of Anat. and Physiol. II. 2. 329.

[2] Gaz. hebdom. 23. 1867.

[3] Sitzung der med. Section der niederrhein. Gesellschaft, in Berliner klin. Wochenschrift. 40. 1865.

Symptoms and Course.

We possess very incomplete reports of the symptoms which have been observed in cases of human poisoning by curare, and we must, therefore, supplement them with the symptoms which appear in experiments on animals.

Preyer, after having swallowed curare powder, felt violent determination of blood to the head, exceptionally violent headache, which, however, was of short duration, and a peculiar weariness and disinclination to move, which lasted for several hours. There was also increase of salivary and mucous secretion. In the case of the young man mentioned by Preyer, the symptoms of poisoning did not set in till five hours after the contact of curarine with the wound; they consisted chiefly in very abundant salivary, sudatory, and lachrymal secretions, increased secretion of nasal mucus, and an increase in the quantity of urine; later on followed an unwonted sense of freshness and relief. Voisin and Liouville[1] induced similar slight effects in a series of patients. They observed that curare acts much more energetically in subcutaneous injection than in endermatic application, but that subcutaneous injection produces very great irritation at the spot where it is applied, creating swelling and violent pain, which may last several days; they frequently observed phlegmonous inflammations produced.

The pulse generally becomes rather more frequent and stronger, often dicrotic, and this dicrotism may last several days. The temperature rises from two to three and a half degrees Fahrenheit. The number of respirations increases four to eight per minute. The quantity of urine is augmented, and it contains sugar; sometimes an erythematous rash appears on the skin. When Voisin and Liouville administered larger doses, they observed more violent symptoms. These usually set in after from twenty minutes to half an hour or an hour; the first symptom was a severe rigor, which, according to the constitution of the patient, may last a longer or shorter time, and which is

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[1] Annal. de Hygiène. Juill. 155. 1866.—Gaz. hebdomad. No. 32–37.—Gaz. des Hôp. No. 109, 111, 114. 1866.

generally very decided, and accompanied with goose-skin, chattering of the teeth, and trembling of the whole body. Then follow disturbances in the circulation, cardiac action becomes more rapid, the pulse more frequent and weak; it may rise for four or five hours to 140. Great anxiety, sighing respiration, increased temperature, and disturbances of vision are also observed. The last consists chiefly of double vision and mydriasis; the latter is by no means constant, but often alternates with myosis. At the same time the lower extremities lose their mobility; the equilibrium can no longer be preserved; the co-ordination of movements is disturbed; the patients can neither stand nor move their legs. This paralysis lasts for a quarter of an hour, sometimes even for an hour. Consciousness and sensation remain intact; great thirst, violent headache, and, in some cases, considerable sudatory secretion are present. Recovery sets in even after such severe symptoms as these. A certain weariness remains, especially in the lower extremities; the increase of temperature may also last a few days.

The most severe forms of poisoning have not been observed sufficiently in detail in human subjects, but such poisonings have been very frequently produced in animals for physiological purposes. When curare has been conveyed into any part of the body of a warm-blooded animal, its head, after some time, falls down, and soon afterwards the whole animal sinks prostrate, without convulsions; curarized animals are no longer capable of raising themselves completely, and after a while all voluntary movement ceases, nor can any reflex movements be aroused even on the application of strong irritants. Respiration becomes steadily slower and weaker, and very soon ceases altogether. The heart still continues to beat strongly, but naturally only for a very short time. In the case of cold-blooded animals—frogs, for instance—the same paralysis sets in, only with them the heart continues to beat for days, while the paralytic condition remains unchanged. In human subjects also this general paralysis occurs, and respiration, in consequence, is arrested, and death rapidly ensues from carbonic acid poisoning. It is impossible to state accurately what amount of curare is sufficient to produce the different degrees of poisoning, as the various sorts of curare

which are offered for sale are not equally rich in the active principle curarine. Voisin and Liouville,[1] by doses of 50 milligrammes (three-quarters of a grain), produced only very slight symptoms, but by 150 milligrammes (two and a half grains), violent ones; but subcutaneous injection of one and a half grains (0.1), four times repeated, failed to produce general severe effects. Rabbits are killed rapidly by less than half a grain (0.025); frogs are paralyzed by minimum doses, but afterwards recover.

Analysis of Symptoms—Mode of Action of Curare-Poisoning.

The most remarkable effect of curare is paralysis of the voluntary movements, and this action has been diligently studied by distinguished investigators, so that a universal concurrence of evidence has been obtained on this important question. Claude Bernard,[2] Koelliker,[3] Pelikan,[4] A. v. Bezold and Heidenhain,[5] and others, have made valuable observations on this subject. The cardinal experiment which gives us direct insight into the action of curare is the following: a frog, when the vessels of one leg have been ligatured, becomes paralyzed over the whole body with the exception of this leg; this leg retains the power of voluntary movement, and can be moved reflexly by stimulation of any part of the animal's skin. Hence it is clear that the paralysis is not central but peripheral, and that sensation remains intact. The muscles which have been deprived of movement by curare react to direct stimulation as in the natural condition; they are, therefore, intact; but the muscle does not react to irritation of the motor nerves. The cause of paralysis must, there-

[1] Loc. cit. and Compt. rend. LXIV. 3. p. 131. 1867.

[2] *Cl. Bernard* and *Pelouze*, Compt. rend. XXXI. 533. 1850; *Cl. Bernard.* Compt. rend. XLIII. 824. 1856; *Cl. Bernard*, Leçons sur les effets des substances toxiques. 1857.

[3] Note sur l'action du curare sur le système nerveux. Compt. rend. XLIII. 791. Oct. 1856; Physiolog. Untersuchungen, etc. Virch. Arch. X. 3 ff.; Zeitschr. f. wissenschaftl. Zoologie. IX. 434.

[4] Virchow's Archiv. XI. 5. 1857; L'Union med. 35. 1857.

[5] *A. v. Bezold* u. *Heidenhain*, Med Centralzeitung. 49, 58, 59, 64. 1858; *A. v. Bezold*, Mueller's Archiv. 2, 3. 1860.

fore, be sought in the motor nerves ; but the nerve-trunk is not altered by curare. For we can moisten a nerve-trunk with solution of curare, and yet by stimulating it produce muscular twitching. But this twitching ceases at once when the muscle is sprinkled with the poison ; therefore it must be the extremities of the motor nerves only which are paralyzed by curare. Thus we find that curare interposes an impediment between the motor nerves and the muscle by paralyzing the intramuscular extremities of these nerves. This action affects all voluntary muscles equally ; therefore it influences the respiratory muscles, and their paralysis must lead to asphyxia. Thus death from curare is shown to be essentially death by asphyxia.

The action of curare on the heart, as we have already mentioned, is not specially prominent, and consists only in accelerating the heart-stroke. This increase of cardiac contractions depends upon paralysis of the extremities of the vagus in the heart, which, indeed, according to v. Bezold, do not yield so rapidly to the action of curare as the extremities of the motor nerves do, but yet with large doses of curare they lose their excitability, so much that irritation of the trunk of the vagus is no longer capable of arresting cardiac contractions. When large doses are in operation, the vessels become dilated through paralysis of the vaso-motor extremities of the nerves, so that, notwithstanding the increased frequency of cardiac contractions, the blood-pressure is lowered. Irritation of the sympathetic in curarized animals causes no dilatation of the pupils (Koelliker and Zelenski[1]) ; but Bidder[2] disputes this statement and asserts that the sphincter iridis is paralyzed, and that consequently the dilatation (sympathicus) predominates, which accounts for the mydriasis usually observed. No attempt has hitherto been made to reconcile these conflicting views. The intestinal movements seem to be more lively and energetic in curarized animals than in the natural condition ; the irritation of the splanchnicus which inhibits the intestinal movements has no effect in animals completely under the influence of curare. This increased peris-

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[1] Arch. f. patholog. Anatom. XXIV. 362.

[2] Arch. f. Anatom. und Physiolog. 1865. 337.

taltic action in the intestine which, according to Dr. Nasse,[1] does not occur if the poison cannot flow through the arteries in the wall of the intestine (from ligature or compression) is indirectly dependent on the paralysis of the splanchnicus, since by this paralysis dilatation of the vessels with increased blood-contents and decreased elimination is brought about, and this vaso-motor influence over intestinal movements is, according to S. Meyer's researches, of great importance.

As regards the increase of salivary secretion, which accompanies most cases of curare-poisoning, we have not lighted upon any clear explanation of it ; Claude Bernard,[2] indeed, succeeded in producing a flow of saliva in animals by the local application of curare to the submaxillary glands themselves, the secretion from the glands becoming continuous. It is probable that in this case also the vessels are paralyzed. The increase of temperature which is observed in the human subject after the application of curare appears inconsistent with the fact, observed by most authorities, that in animals the temperature is lowered. The increase of temperature in human beings can only be explained by supposing that the small doses of curare which have been introduced cause a contraction of the vessels, thus tending to diminish the loss of heat. When once the vessels become paralyzed the temperature must naturally diminish, as with animals. But this stage is never reached in human beings, because asphyxia sets in so rapidly. The influence of curare on the sensory nerves is extremely slight, and, if we ligature the artery of a leg and so exclude it from contact with the poison, we can, in animals otherwise paralyzed, produce movement in this unpoisoned leg by irritation of the sensory nerves. Therefore the excitability and conductibility of the sensory nerves, as well as the reflex excitability of the spinal cord, are retained in ordinary cases of poisoning. If, however, very large quantities of curare are employed, and life is maintained by artificial respiration, the spinal marrow then becomes affected, its excitability being at first increased and subsequently paralyzed. Testimony to this

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[1] Beiträge zur Physiologie der Darmbewegungen. Leipzig. 1866. 61.

[2] Journ. de l'anat. et de la physiolog. 1864. 507.

effect is found in the writings of A. v. Bezold,[1] Wundt and Schelske,[2] and in those of Magron and Bouisson;[3] the motor cardiac centres are also similarly affected by large doses of curare (v. Bezold); they are first excited and later on paralyzed. The question whether the conductibility and excitability of the nerve-trunks are affected by large doses of curare is answered in the affirmative by v. Bezold, who observed that when means are taken to bring the motor nerves under the influence of curare, while their muscles are protected from its influence, they convey the stimulation which they have received more slowly to the muscle than when in their normal condition. Thus we find that curare is a poison which primarily paralyzes the extremities of the motor nerves of the voluntary muscles, and later on those of the involuntary muscles and of the vessels, and which tends to cause death by producing paralysis of the respiration; at a later stage and secondarily, the nerve-trunk, the spinal cord, and the motor apparatus of the heart, after initial increase of excitability, also become paralyzed. Its secondary action can only be observed in experiments on animals and by keeping up artificial respiration, because in human subjects death supervenes before these symptoms can be developed. It is not yet ascertained how the presence of sugar in the urine is brought about by curare; and interesting as this question is in itself, its significance in practical toxicology is so subordinate that we are quite justified in dismissing it without further consideration. It is most probable that it is a result of disturbances in the circulation.

Results of Autopsies.

No reports of autopsies on human beings have come within my knowledge; in animals we find the usual signs of death by asphyxia. The blood also, when submitted to spectrum analysis, only shows signs of accumulation of carbonic acid (Preyer[4]).

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[1] Mueller's Arch. 2. 3. 1860.

[2] Verhandlungen des natur-histor. med. Vereins zu Heidelberg. II. 1. 1860.

[3] Compt. rend. XLVIII. Nov. 4. 1859; and Journ. de la Physiol. II. 7. 8. 1859.

[4] Berlin klin. Wochenschrift. 43. 1867.

The statement of J. Hoppe,[1] that curare produces hyperæmia in various organs, but never in the spinal marrow, is not inconsistent with the condition usually found after death by asphyxia.

Diagnosis and Differential Diagnosis.

The recognition of curare-poisoning as such depends on the existence of paralysis of the voluntary muscles with diminished frequency of respiration, while the cardiac action and the sensorium remain unaffected. The diagnosis will, however, be rendered more certain if, in examination, it is found that the patient has been wounded by a poisoned arrow, or if the history of the case can be obtained. It is very easy to confound curare-poisoning with poisoning by coniine. In Europe, when the question is in doubt, the probability is in favor of coniine-poisoning, especially when there is no external wound.

Prognosis.

The prognosis of curare-poisoning will be favorable if the system is under the influence of only small quantities of the poison, and especially, therefore, when the poison has been introduced internally by the mouth. The early summons of medical aid will often have a considerable influence on the issue of the case. The prognosis is unfavorable if large quantities of the poison have been rapidly absorbed into the blood. The slower the absorption from a wound or from the stomach, the more favorable is the course.

Treatment.

Although curare acts so powerfully on the organism, yet treatment is by no means ineffectual in counteracting its influence. Small doses taken internally are of no consequence, as they produce no symptoms; large and poisonous doses should, if possible, be eliminated by emetics. The remedies recom-

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[1] Wiener Zeitschrift. Oct. Nov. 1857.

mended as antidotes, tannin and iodine, certainly do throw down precipitates with solutions of curare, but they are themselves not innocuous. If there is a surface wound through which curare has been introduced, the limb affected should at once be ligatured above the wound, *e. g.*, with a caoutchouc band, or with an ordinary strong bandage, and the wound should then be washed. If, after some time, no symptoms of poisoning appear, the bandage may be unfastened, and the blood allowed to circulate again in the affected limb. But the ligature must be renewed again quickly, so that as little of the poison as possible may be conveyed into the general circulation, and the residue retained in the wounded limb. If symptoms of poisoning appear after the bandage has been loosened, we must reapply the bandage and wait till they subside, after which we may readmit the isolated blood into the general circulation, and follow this plan till all symptoms have disappeared. We may thus succeed in preventing paralysis and preserving life in animals, after large quantities of curare have been subcutaneously injected into the lower part of a limb. If threatening symptoms set in, as slow respiration, dyspnœa, anxiety, etc., attention must be directed to the respiratory process, and it must be kept up by stimulants, but especially by artificial respiration. Thus animals who had been poisoned with large doses of curare have been saved by continuous artificial respiration. According to Bert's[1] researches, animals may be saved even when twice the quantity necessary to destroy life has been subcutaneously injected. But if a still larger dose has been introduced, even artificial respiration will be of no avail, because such doses cause paralysis of the central organs, the spinal marrow, and the motor cardiac ganglia. In practice we shall find that stimulants, etc., may be advisable, in addition to artificial respiration.

Changes which Curare undergoes in the Animal Organism.

The active constituent of curare is readily soluble in water, and therefore readily absorbed into the blood; this absorption

[1] Empoisonnement avec le curare. Gaz. méd. de Paris. 11. p. 148. 1869.

takes place very rapidly from the subcutaneous tissue; absorption also takes place from the mucous membrane of the stomach and intestine, from the conjunctiva, etc., but much more slowly than from the subcutaneous tissue. The curare which has been absorbed into the blood is very soon eliminated from the organism again, principally through the urine, without having been decomposed in its passage through the body, or having suffered any alteration. Thus the urine of a curarized frog will poison another, and with its urine we can poison a third, and so on. But this cannot be done with any other fluid of the body, the bile, for example.[1] It is upon the rapid excretion of curare that we depend for the favorable result of ligaturing the part of the body where the poison has been introduced, and of artificial respiration, which maintains life till the poison has left the body. It is also by the rapid excretion of the poison that we account for the remarkable fact that doses which, injected subcutaneously, produce very serious symptoms, when taken into the stomach have no effect. A wound poisoned by curare may be sucked without any danger. These facts led to the belief that the poison was inoperative when taken into the stomach, and either was not absorbed or suffered decomposition there. All these hypotheses are false; curare is slowly absorbed, but is so rapidly excreted again that usually the blood is not sufficiently charged with curare to induce symptoms of paralysis. It has been shown by several investigators, *e. g.*, Cl. Bernard, L. Hermann, and others, that if the renal arteries of an animal are ligatured, and if then curare is given by the stomach, symptoms of poisoning set in, just as in subcutaneous injection, only more slowly. In this case the excretion of the poison by the kidneys is prevented, and curare is retained in the blood in sufficient quantity to produce the characteristic symptoms. Koch[2] discovered that the liver of animals poisoned with curare contains a relatively large amount of curarine, and concluded therefrom that the liver absorbs the poison conveyed to it through the

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[1] *Bidder*, Reichert's Archiv. 1869. p. 598.

[2] Versuche über die chemische Nachweisbarkeit des Curarins in thierischen Flüssigkeiten und Geweben. Dorpat. 1871. Dissert.

mesenteric vein and retains it for some time, so that only small quantities at a time return into the general circulation ; in this way he explains the remarkably little effect produced by curare when taken by the stomach. Though the greater proportion of the poison introduced is excreted in the urine, a considerable portion also passes off in the fæces, as appears from Koch's researches. So long as curare circulates in the blood, it appears to be distributed pretty equally everywhere, with the exception of the liver, as mentioned above ; thus Koch found it in almost all the organs and also in the blood itself.

Chemical and Physiological Tests.

We must search for evidence of the poison, when it has been internally administered, especially in the matters vomited, the urine, and the fæces. If the poison has been endermatically or subcutaneously applied, we must examine the urine in the first place, and then the fæces. In fatal cases, the liver must also be carefully examined.

For separating the poison from organic substances, the Koch-Dragendorff method is the most desirable to follow. Add alcohol to the acidulated watery extract to throw down the dissolved albumen, mucous and coloring matters. Shake the filtrate repeatedly with benzol, or, better still, with amylic alcohol. Evaporate the latter to the consistence of syrup, and add alcohol at 95%. Now filter, add to the filtrate baryta water in excess, and throw down the excess of baryta with carbonic acid. Now evaporate the filtrate in a water-bath to dryness, and from the residuum dissolve out the curarine with water. In this way a brownish-red or yellow solution is obtained, to which the physiological test of the poison may be applied. In order to obtain curarine sufficiently pure for the chemical reactions, Koch recommends that we should mix the watery solution with powdered glass and dry it, and then leave it for a long time in contact with chloroform. The chloroform then leaves the curarine behind in a sufficiently pure condition to be recognized chemically as such.

The following are the chief reactions of curarine: concen-

trated sulphuric acid gives to solutions which contain even one-sixteenth of a milligramme (one-thousandth of a grain) of curarine a red color, which later on becomes darker, and after about four hours appears rose-colored and is recognizable even after twenty-four hours. Concentrated sulphuric acid and potassium bichromate bring out, as in strychnine, a beautiful blue color, which passes into violet, and later on into cherry-red. This transition is slower in curarine than in strychnine. If a solution of curarine or of curare be heated with dilute sulphuric acid (1 : 50) in a water-bath, the solution becomes reddish, then purple, and later on, with longer heating, black.

The physiological test for curarine is more valuable and easier of application. Inject some of the substance to be investigated subcutaneously into a frog or a rabbit, and observe the symptoms of paralysis of the muscular apparatus which after some time set in, and to which the rabbit succumbs, whereas the frog generally recovers.

Poisoning with Opium and Morphine.

Opium and morphine are used so frequently as poisons that they possess on that account the greatest interest for the physician. The two substances resemble one another so entirely in their effects, that in a manual of practical toxicology, which is to serve as a guide for the practical physician, it will be as well to treat of them together, and by so doing we shall avoid repetition.

Morphine ($C_{17}H_{19}NO_3$) is a crystallizable alkaloid, the salts of which are readily soluble in water; pure morphine is sparingly soluble in water, and insoluble in ether. It is the chief constituent of opium, in which it is contained in various proportions from 2.8 per cent. to 20 per cent., according to the kind of opium, the country from which it is obtained, the time of gathering, etc. East India opium contains the smallest quantity of morphine, 2 per cent.; the greatest amount is found in that cultivated in Europe, 20 per cent., *e. g.*, that from Provins, Erfurt, etc. The ordinary opium sold by chemists, *i. e.*, Egyptian or Smyrna

opium, contains between 10 and 13 per cent. of morphine. The German [and U. S.] Pharmacopœias require that the opium used in medicine shall contain a minimum quantity of 10 per cent. of morphine. As so large an amount of morphine is contained in opium, the poisonous effects of opium are the same as those of morphine. Still opium-poisoning differs in some subordinate points from morphine-poisoning, because opium contains, in addition to morphine, a number of other substances, partly alkaloids, partly also resinous, gummy, and acidulous bodies, besides fat, sugar, extractive substances, and salts, which modify the effect of it, and in different degrees, according to the proportion in it of these different substances.

Narcotine is the ingredient of next importance, as regards quantity, in opium (which, as is well known, is obtained by inspissating the milky sap of the seed-capsules of Papaver somniferum), and this is present in opium in the proportion of from 5 to 10 per cent.; it is worthy of notice that those kinds of opium which contain most morphine contain least narcotine, absolutely as well as relatively, and *vice versa*, so that many have imagined that narcotine is converted into morphine. Narcotine ($\Theta_{22}H_{23}N\Theta_{3}$) is a crystallizable alkaloid which is almost insoluble in cold water, sparingly soluble in warm water, readily soluble in benzol, amylic alcohol, hot alcohol, and ether, and most readily of all in chloroform. In our present state of knowledge as to the action of narcotine, it must be characterized as having, on the whole, the same kind of action as morphine or opium, but in a less degree.

Narceïne ($\Theta_{23}H_{29}N\Theta_{9}$), an alkaloid which may be extracted from opium in the proportion of one-tenth of one per cent., has a similar effect to narcotine, but more powerful. Narceïne in a pure condition is sparingly soluble, whereas its salts are readily soluble. This substance also is quite subordinate in its action to morphine. The same holds good with regard to *codeïne* ($\Theta_{18}H_{21}N\Theta_{3}$), which exists in opium in the proportion of from one-quarter to three-quarters of one per cent. This is not very readily soluble in water, but is readily soluble in alcohol, ether, and chloroform. This substance bears a close resemblance to morphine in its mode of action.

Thebaïne ($C_{19}H_{21}NO_3$) is found in the proportion of about one per cent. in opium; it crystallizes like the alkaloids mentioned above, is readily soluble in alcohol and ether, sparingly so in water; thebaïne acts as an irritant upon the central nervous system, so that it produces tetanus as strychnine does. This substance, with regard to its physiological action, differs widely from that of opium and morphine, but it is contained in opium in too small a proportion to modify in any special manner the symptoms of opium-poisoning.

The action of *papaverine* ($C_{20}H_{21}NO_4$) is to some extent antagonistic to that of thebaïne. This alkaloid is insoluble in water, but very readily soluble in hot alcohol; it is a powerful agent in inducing sleep, and paralyzes the motor centres (W. Baxt).

Of the substances contained in opium, there still remain to be mentioned pseudomorphine, metamorphine, opianine, porphyroxine, cryptopine, rhœadine, papaverosine, meconine, meconic acid, caoutchouc, etc., which may be obtained from it in small quantities, and none of which exercise any important share in the physiological action of opium.

It has been already said that all the alkaloids of opium do not act in the same way; but some, and those the majority, have a decided influence in diminishing the excitability of certain special portions of the nervous system, whereas others increase the excitability of the nervous system. Tables have been drawn up, classifying the alkaloids of opium according to their action. Thus Claude Bernard,[1] who has devoted himself successfully to the investigation of the action of the opium alkaloids, has drawn up the following table, at the head of which are the alkaloids which have the most powerful paralyzing action, and at the other end those which act most strongly in producing convulsions: Narceïne, Morphine, Codeïne, Narcotine, Papaverine, Thebaïne. A second series has been drawn up by Waldemar Baxt,[2] who regards papaverine as the most paralyzing poison, and therefore places it above narceïne.

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[1] Compt. rend. LIX. 1864. p. 406. et seq.

[2] Zur physiologischen Wirkung der Opiumalkaloide. Arch. f. Anat. und Physiol. p. 112 ff. 1869.

As the proportions of the paralyzing substances in opium far exceed those of the exciting substances, the characteristic of opium-poisoning is its paralyzing effect; and indeed it is these paralyzing qualities which demand the attention of practical toxicologists, as we learn from a vast number of cases that opium and morphine are almost the only poisons used in ordinary life, so that it appears necessary, for a variety of reasons, to consider them.

Etiology.

Poisoning by opium and morphine occur whenever substances containing opium and morphine in excessive doses are introduced into the organism, and become incorporated with the blood. Such substances are, in the first place, opium itself, and the medicinal and pharmaceutical preparations prepared from it: extract, tincture, and wine of opium; syrup of poppies; morphine and its salts, especially the hydrochlorate, sulphate, and acetate; also the leaves, seeds, and seed-capsules of the poppy,[1] which have been administered in infusions or decoctions, especially by lazy nurse-maids to the infants under their charge, to put them to sleep. Children have also been poisoned by eating the blossoms and fruit of the Papaver Rhœas.[2] We have an immense number of cases reported in modern times of poisoning, in England and America, from the use of nostrums containing opium and morphine: Black drops, Godfrey's elixir, Dalby's carminative, Battley's sedative solution, etc. All contain opium, and may cause poisoning as effectually as the other preparations of opium used in medicine. The poisoning produced by these drugs is mostly medicinal, caused by carelessness in prescribing[3] or dispensing, or they have arisen out of other accidents, *e. g.*, mistaking one drug for another in chemists' shops; thus a number of cases of poisoning by morphine have been published in late years (at

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[1] *A. Chevallier*, Journ. de chimie médic. Août. p. 365. 1869; *Sulzmann*, Badische ärtzl. Mitthlg. 1868.

[2] *Palm*, Würtemberg. med. Corresp.-Blatt. 1855. No. 33.

[3] Thus the Journ. de chim. méd. p. 139. 1868, relates a case of fatal poisoning, caused by the doctor's ordering, in his hurry, 12 grains of morphine instead of ½ a grain.

Vienna, Berne, Carlsruhe, etc.), which have arisen partly from dispensing chemists confounding drugs, and giving hydrochlorate of morphine instead of hydrochlorate of quinine, partly through confounding the substances in the manufactory which furnished them. Opium and morphine have been largely used for committing suicide, especially by medical men, chemists, etc. Morphine has also been used with the intent to murder, as we learn from the case of Dr. Castaing,[1] although it would appear, from its bitter taste, ill-adapted for this purpose. There are also instances of persons who have been stupefied by opium and morphine in order to rob them more easily; and there are many cases of poisoning described in which tincture of opium instead of tincture of rhubarb has been taken in tablespoonful doses.

The manner in which the poison is conveyed into the system is comparatively unimportant; cases of poisoning have been observed not only from the internal administration, but also from morphine and opium being used in the form of enemata or suppositories, or even by endermic or subcutaneous application; even simple fomentations[2] with opium on the healthy, uninjured skin have produced symptoms of poisoning.

The symptoms of poisoning naturally appear early, if the poison has been rapidly absorbed into the blood. This absorption, especially in cases of internal administration, is, however, dependent on a series of factors: the fulness or emptiness of the stomach is an important one; the emptier the stomach, the more rapid the absorption; the form in which the substance has been administered is also an important consideration. Opium powder acts more slowly than tincture of opium, pure morphine more slowly than hydrochlorate or acetate of morphine, which is the most rapidly dissolved; the effect of subcutaneous injection is very rapid; when the poison is injected into the veins the symptoms set in almost instantaneously.

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[1] *Castaing* poisoned his friends, the brothers Ballet, in 1822 and 1823; the death of the latter was caused by morphine and tartarized antimony; he was condemned at Paris. Also at Lambeth workhouse, in London, according to Pharmac. Journal, p. 597, 1868, a man seems to have been intentionally poisoned with morphine by an attendant.

[2] *Taylor* relates in his work "On Poisons," translated by Dr. Seydeler, III. Vol. p. 16, a case in which a soldier died in consequence of fomentations which he had to apply to an erysipelatous leg, and which had been moistened with an ounce of laudanum.

It is impossible to state accurately what quantities of opium and morphine are sufficient to cause death. A strongly marked difference exists between the cases of adults and children; the latter in the first years of life are very susceptible to the action of opium.

As regards adults, John Dougall[1] relates a case of suicide in a woman, who took one drachm (= about 4.0) of tincture of opium and died notwithstanding medical treatment.

According to Taylor,[2] the smallest dose of opium in substance known to have caused the death of an adult is two and a half grains of extract of opium, equal to four grains of raw opium. Of morphine, naturally, much smaller doses are fatal; a dose of even one and a half grains (0.1) of a salt of morphine may prove very dangerous.

But daily experience and many clinical cases that have been published prove that much smaller doses of opium and morphine may produce violent symptoms of poisoning without actually causing death.

The individual constitution plays a very important part in narcotic poisoning; for example, there are cases of persons who have recovered even after enormous doses of opium and morphine; thus Taylor mentions in his manual (loc. cit.) cases which ended in recovery, although four and five ounces of tincture of opium had been taken. In a later case given by Bare,[3] a man, who had taken ten drachms of tincture of opium (= 40.0), recovered without vomiting.

Cases are also reported of recovery after large doses of morphine. Bonjean[4] witnessed a recovery after twenty-five grains (= 1.5) of acetate of morphine. Bergsten[5] saw an apothecary recover after six grains (0.4) of morphine acetate; Lyons[6] reports the recovery of a girl, five years of age, who had been poisoned with four and a half grains (0.3) of morphine.

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[1] Glasgow Med. Journ. May. p. 339. 1872.

[2] "On Poisons," translated into German by Seydeler. 1868. Vol. III. p. 25.

[3] Philadelph. Med. and Surg. Reporter. Jan. 6. 1869.

[4] See *Husemann*, Handbuch der Toxikologie. I. Vol. p. 597. 1863.

[5] Läkare fören Förhandlungen. VII. p. 647. 1872.

[6] New Orl. Journ. of Med. p. 293. 1869.

Certain diseased states seem to blunt the effect of opium, so that colossal doses are often borne. To these belong all forms of mental alienation. In a case related by Model,[1] a female maniac took eighteen grains (= 1.1) of acetate of morphine, and was found pulseless and scarcely breathing, yet she recovered completely after a few hours. Kellok[2] gave a woman suffering from puerperal mania, thirty grains (= 1.9) of morphine muriate in twenty-four hours, without any consequent poisonous effect. On the other hand, I myself witnessed a case in which a woman suffering from maniacal attacks, had about three grains (= 0.18) of morphine subcutaneously injected in the course of two hours, without being quieted: sleep and collapse set in after two hours, in which the patient sank. Further, it is well known that in tetanus, delirium tremens, hydrophobia, and poisoning by strychnine and atropine, very large doses of opiates are borne; the same is the case with cancer, peritoneal diseases, neuralgia, etc. A mighty influence is also exercised by custom. There are persons, especially those suffering from chronic diseases, who from small doses of opium go on to larger and larger doses, in order to obtain sleep or a few hours' freedom from pain, and who bear doses which would speedily destroy life in healthy people. Every hospital and almost every physician has such cases to report.

It is needless to say that such persons require enormous doses of opiates to produce poisonous effects, as the system has become accustomed to the poison.

On the other hand, there are persons who are highly sensitive to opiates, and are made severely ill by even small doses; this we call *idiosyncrasy*. Thus Christison[3] speaks of a man who was thrown into a state of sopor by from one-third to one-half of a grain (= 0.02 to 0.03), and Steinthal[4] witnessed a serious case of poisoning from one grain (= 0.06) of opium, administered in an enema.

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[1] Bayr. Intelligenzblatt. No. 46. p. 572. 1871.

[2] See *Husemann*, loc. cit.

[3] See *Husemann*, Toxikologie I. Vol. p. 597.

[4] See *Husemann*, loc. cit.

In Donyan's[1] case $\frac{1}{32}$ of a grain (= 0.002) of morphine endermically applied produced violent narcotism, hemiopia, etc. In the *Lancet* of March 21, 1863, a case is described in which a woman, four or five hours after taking two drops of laudanum, was seized with rigors, loss of sight and hearing, and became covered with a rash resembling scarlet fever.

It is remarkable, that poisoning often occurs from doses which have often at other times been given without any particular result. Perhaps this may depend on accidentally rapid absorption. It cannot certainly be a case of cumulative action.

On the other hand, we find on record a long series of recoveries after large, and even very large, doses of opium, quite apart from cases in which perhaps the greater part of the poison has been eliminated before it was absorbed, therefore, before its action began.

Children assume a special position with regard to opiates.

We may say in general, that the younger children are, the more sensitively they react to opium and morphine. They retain this sensitiveness during the first year of their lives, and sometimes even up to five years of age. A number of cases have been published, in which minimum doses of this poison have proved fatal to children. Taylor[2] has collected a number of such cases, in which $\frac{1}{90}$, $\frac{1}{12}$, $\frac{1}{8}$ of a grain of opium, or one, two, three, and four drops of tincture of opium caused death. In a case given by Schmidt,[3] $\frac{1}{20}$ of a grain (= 0.003) of opium caused the death of a child.

And yet cases are not wanting in which much larger doses have been borne by children, without killing them. Thus in Corbet's[4] case, thirty drops (= 1.9) of laudanum were administered to a newly-born child: very alarming symptoms followed, and yet recovery set in after five hours. In a case mentioned by Blank,[5] a little boy three weeks old, to whom three enemata

[1] Empoisonnement par une dose extrêmement faible de morphine. Gaz. des Hôpit. 1844.

[2] On Poisons, etc. Vol. III. p. 29 ff. of Seydeler's Translation.

[3] Gaz. des Hôpit. No. 16. 1855.

[4] Lancet. II. 9. Aug. 1857.

[5] Rev. de thérap. méd. chirurgie. 17. 1857.

with thirty-five drops of laudanum each had been administered, recovered the following day, notwithstanding very violent symptoms. Another child [1] took a teaspoonful of tincture of opium, and recovered under simple treatment. It will thus be seen that it is scarcely possible to fix the doses of opium or morphine which must be regarded as fatal.

As soon as a sufficient quantity has entered the circulation, to disturb the functions concerned, symptoms of poisoning set in. The period of the appearance of the first symptoms varies considerably.

Pathology.

Symptoms and Course.

The group of symptoms produced in human subjects by opium or morphine may serve as the prototype of all simple narcotic poisonings. The ordinary sequence of the symptoms corresponds with a reduction of the excitability of the nervous centres, preceded by a longer or shorter stage of increased excitability. As soon as a sufficient quantity of the poison has entered the circulation, a condition of mental excitement of a pleasurable character sets in, physical activity, restlessness of the limbs, rolling of the eyeballs, acceleration of cardiac action, sometimes hallucinations of a cheerful and agreeable nature: at the same time there are dryness in the throat, increased thirst, and occasionally sexual excitement. Whether the doses have been considerable, or only such as are usually ordered medicinally, this condition never lasts long; it is gradually replaced by headache, weariness, a sensation of weight in the limbs, incapacity for exertion, sleepiness, disturbed sleep, diminution of sensibility, and generally great contraction of the pupils. In this semi-somnolent stage, circulation and respiration remain normal.

But soon this state, from which the patient may be roused, or during which he may even be kept awake by speaking to him in

[1] *Plum*, Hospit. Tidschr. 1868.

a loud voice, shaking him, or by communication of pain in some way, passes into complete coma. The patient lies motionless on his couch, cannot be awakened; sharp blows make no impression upon him; reflex action ceases altogether; the eyes are generally half shut; the pupils are strongly contracted (very rarely dilated), and do not react to light; the muscles are relaxed; if one of the limbs is lifted up it falls back as if paralyzed, the lower jaw falls, the skin is cold to the touch, the appearance of the patient is either pale and livid or dark and cyanotic—in short, he is like a dead man, respiration and pulsation being the only signs of life; but these functions also have suffered considerably under the influence of the poison; respiration has become slow, labored, irregular, and stertorous; it may even be accompanied by various mucous râles; the action of the heart has become slower and more irregular, the pulse is more feeble, very compressible, often difficult to feel; still, under favorable circumstances, the patient may awake out of this stage of complete narcosis and recover.

But in the most serious cases the symptoms are still more aggravated. The respiration and the pulse become still slower and feebler, the cyanosis increases, the skin becomes colder and covered with cold perspiration, the noisy râles increase, certain muscles and groups of muscles manifest tremulous, clonic twitchings of short duration; the pupils are frequently dilated in this stage, sometimes, though rarely, actual trismus and tetanus set in; salivation is also observed in some instances.

And thus death may slowly supervene with gradual extinction of the pulse and respiration, or paralysis is rapidly developed, and collapse puts an end to suffering. Cerebral hemorrhage sometimes occurs during the progress of the case, and this itself may ultimately prove fatal. One constant symptom through the whole course of the case is suppression of the urine and fæces, but sometimes, especially at the beginning and the close of the case, we may meet with marked symptoms of strangury. In almost all cases of opium- and morphine-poisoning we meet also with very profuse perspiration.

When the case takes a favorable turn, the first sign of improvement is in the respiration and pulse becoming more regular;

blood-pressure increases, while the comatose symptoms gradually subside and are replaced by a lighter soporific state, out of which the patient can be roused, though it may often last twelve to twenty-four hours. But cases have occurred where the patient had been completely roused, and there was hardly any doubt of eventual recovery, which nevertheless ended fatally from the relapse into stupor, sopor, and coma, and finally paralysis. It is very probable that in these cases there is a renewed absorption of poison, perhaps under the influence of increased blood-pressure. Again, cases are on record in which, after the symptoms of acute opium- and morphine-poisoning had completely disappeared, death supervened from affections of the heart or the lungs. In these cases it is highly probable that heart-disease existed previously to the introduction of the poison, and that under the influence of the poison the heart became paralyzed, and death followed from asphyxia. In such cases, therefore, opium-poisoning is only a secondary cause of death, and it does not follow that the patient is narcotized at the moment of death. Taylor relates some such instances,[1] and one especially (A. Stafford) is important, because the patient was able to undertake a journey on the sixth day after the poisoning, and did not die till the eleventh day. He had been bled for gall-stone and had lost thirty ounces of blood, and had taken in four hours 200 drops of laudanum and 200 drops of tincture of hyoscyamus. At the autopsy serum was found effused in the pleura, in the pericardium, and in the subarachnoid space; the heart was found to be enlarged, with very soft, thin walls in a state of fatty degeneration. Here death was certainly not the result of opium-poisoning, but arose from heart-disease, for the heart, especially after so much blood had been withdrawn, could no longer, under the influence of opium, contract with energy, and thus opium was indirectly responsible for the fatal result. More recently a case has been reported by Duchek,[2] in which the symptoms of poison intermitted for five days; in the morning the sopor had generally disappeared, but in the evening it

[1] Loc. cit. pp. 10, 11, 12, 13. III. Vol. (Seydeler's translation).

[2] Wiener Wochenblatt. XVII. 43. 1861.

recurred very strongly, attended with alarming disturbances of circulation and respiration. Complete recovery did not set in till the thirteenth day.

Certain cutaneous symptoms appear occasionally in opium- or morphine-poisoning, but are not constant. Before the soporific stage sets in the patient often complains of violent itching of the skin, which is quite unendurable, and which is often followed by an exanthem, which consists of wheals, and has a complete resemblance to urticaria; but this form is not strictly maintained, for it sometimes appears as papulous and roseolous patches. Steinboemer[1] mentions the occurrence of a vesicular eruption after one-sixteenth of a grain (= 0.004) of morphine; one-eighth of a grain of opium produced the same eruption. It lasted about eight days, and in the first case was confined to the front of the left arm, which was at the same time swollen.

An exanthem resembling scarlatina appeared in the face, arms, hands, neck, legs, etc., of a lady[2] five hours after she had taken two drops of laudanum; she was also seized with rigors and loss of sight and hearing for some time.

Vomiting is not a constant, but under certain circumstances a very important symptom. In many cases spontaneous vomiting sets in soon after the introduction of the poison, and thus any opium or morphine remaining in the stomach is eliminated, and in many cases this contributes to eventual recovery. Frequently, however, a condition of nausea with repeated vomiting comes on towards the close of the case. In children who have been poisoned with opium, convulsions of various muscles are very frequently observed. Strabismus and convulsions of the facial muscles have been especially observed; and even trismus and tetanus, chiefly in the form of opisthotonus, have been noticed.

In adult males priapism sometimes appears during the stage of narcosis, but more commonly in that of excitation.

It is difficult to say what is the precise length of time from the introduction of the poison to the beginning of the symptoms

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[1] Schuchardt's Zeitschrift. p. 367. 1866.

[2] Lancet. March 21. 1863.

of poisoning. Whereas in the cases reported by Nussbaum[1] and Woodhouse Braine,[2] in which poisoning occurred through the accidental injection of morphine into the venous system, most violent symptoms were developed in a few seconds: congestion in the head, violent cardiac palpitation, throbbing of the carotids, giddiness, sensations of faintness, anxiety, dyspnœa, convulsions of the facial muscles, sudden falling down as if dead; in ordinary injection into the subcutaneous cellular tissue, about five minutes elapse before its action begins to make itself felt. When the poison has been conveyed into the stomach, the symptoms set in later, perhaps after ten to fifteen minutes; with tincture of opium it requires a longer time, with opium powder longer still. A full or empty state of the stomach has, of course, a decided influence. It is of more importance, in connection with medical evidence in courts of justice, if we could say definitely up to what period the poisoned person is still capable of responsible acts; from this point of view there is an interesting case given by Taylor,[3] which proves that a man who had been poisoned with opium had time enough to hang himself; and another case, in which a man who had taken half an ounce of laudanum was able to converse animatedly with his neighbor two hours afterwards.

An interesting case is given by Norris,[4] in which an apothecary, who had taken seventy-five (?) grains (= 4.7) of morphine muriate, was able to walk for an hour and a half before symptoms of poisoning set in; he then recovered under a combined treatment, during which he took fifty grains of extract of belladonna. Opium and morphine introduced by the rectum also acts with considerable rapidity, and produces symptoms as violent as when taken into the stomach.[5] As to the time during which the influence of the poison may last, much may be gathered from what we have already said.

As a general rule, we may say that poisoning by morphine

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[1] Bayr. ärztl. Intelligenzblatt. 1865. p. 36.

[2] Med. Times. Jan. 4. p. 8. 1868.

[3] Loc. cit. III. Vol. p. 9.

[4] Hays' Americ. Journ. 1862. October.

[5] *Alden*, Philad. Med. Times. May 15. 1871.

lasts the longer, the larger the dose, the more complete the absorption, the less the vomiting, and lastly, the less the patient had been accustomed to opiates.

Sometimes the stage of excitement lasts a long time; it is generally shorter comparatively in the case of Northerners than in that of Orientals, with whom these symptoms of excitement persist for a long time. Thus Christison in his book on poisons mentions a case in which excitement lasted eighteen hours after two ounces (= 60.0) of laudanum had been taken, and not till then did somnolence set in. John S. Boyd[1] describes the case of an insane person, in whom two ounces (= 60.0) of laudanum after twenty minutes produced no effect, and it was not till fourteen hours after that somnolence appeared; death supervened sixteen hours later. The stage of narcosis generally lasts twelve to eighteen to twenty-four hours. According to Christison, death occurs between eighteen and twenty-four hours after morphine-poisoning; but cases have been observed in which death supervened much later; thus W. Boyd Muschet[2] relates the case of a child, three months old, who did not die for fifty-six hours after taking an indefinite dose of opium; in the interval a short remission of the symptoms had taken place. If death is not the result, it may be very long before real recovery sets in; thus we find a case in the *Lancet*, in which a woman, thirty-nine years of age, after taking three drachms (= 12.0) of laudanum, did not recover till the fourth day, notwithstanding the use of belladonna. If morphine-poisoning takes a favorable turn, recovery is generally complete, very seldom incomplete. In incomplete recovery some symptoms remain behind for a longer or shorter time. In the first place nausea is to be included among these, then loss of appetite, impaired digestion, feeling of weariness, headache, giddiness, uncertainty of movements; all these symptoms disappear after some time (hours); it is needless to say that if sanguineous apoplexy should occur during the action of the poison, the disturbances depending on this will not disappear.

[1] Brit. Med. Journ. Oct. 10. 1868.
[2] Medic. Times and Gaz. March 20. 1858.
[3] Lancet. Sept. 1868.

Besides the exanthemata mentioned above, a number of other symptoms deserve notice: as contraction of the pupils,[1] which may last some days; slight albuminuria,[2] numbness[3] or tingling of the fingers, flexion of the thumbs; in another case a lady poisoned by a very large dose of tincture of opium, by enema, could neither taste nor see for several days after her recovery.[4]

There frequently remains, especially in opium-poisoning, a tendency to obstinate tenesmus for some time, and this is the most noticeable sequel of opium-poisoning.

Chronic Opium- and Morphine-Poisoning.

The habitual use of opiates, whether medicinally or from a bad habit, leads to chronic opium-poisoning. By far the greater number of cases of chronic poisoning occur in the East and Asia, especially China, India, Persia, and Turkey. In these countries opium-eating, as well as opium-smoking, is very common; we learn how often this custom has been the subject of medical treatment from the reports of James Johnston,[5] who had occasion to treat about 300 cases of opium-poisoning, seventeen of which were severe and six mortal, in the Chinese Hospital at Shanghai. What the consumption of opium in these countries is appears from the following figures:[6] at Samarang, a town with 1,254,000 inhabitants, the average quantity of opium consumed monthly is 7,980 pounds. The town of Japava, with 671,000 inhabitants, consumed, in fifteen days, 5,389 pounds of opium. In the year 1850 over 576,000 pounds of opium were imported into Java; that is, one-eighty-second of a pound per head;[7] it is impossible to calculate how much was smuggled. But in the West also, especially in England,[8] and chiefly in the so-called manufacturing

[1] *Model*, loc. cit.

[2] *Olivier*, Gaz. des Hôpit. p. 124. 1871.

[3] *Woodhouse Braine*, loc. cit.

[4] *Finlay*, Lancet. No. 21. 1868.

[5] Med. Times. 1872 and 1873.

[6] Archiv für Pharmazie. p. 559. 1873.

[7] *Van Dissel*, Med. Times and Gaz. May 18. 1867.

[8] *Hawkins*, Pharmac. Journ. Feb. p. 396. 1868.

districts, in Lincolnshire and Norfolk, opium-eating is constantly on the increase. In these districts an apothecary sold, in one year, 200, another, 140 pounds of opium. The causes assigned for this opium-eating in England are the ill-nourished condition of the lower orders, and the frequency of painful illnesses, needing the prolonged administration of opium, after the cessation of which the custom of taking opium was continued.

Since the subcutaneous injection of morphine has become general, this also begins to spread as a bad habit. Here also the first injections are usually for the relief of painful affections; but after a time the patients become dependent on the injections, and cannot do without them, so that a considerable number of morphine injectors have sprung up—chiefly young doctors—who carry on this pernicious practice, as well as patients themselves, who have been intrusted with the injection-syringe by their doctors.

Chronic opium-poisoning produces a series of symptoms which are tolerably constant, and are described by a number of medical men and travellers. The most prominent symptoms are general emaciation, a pale, shrivelled complexion, relaxation of the muscles, failure of the appetite, disturbed digestion; at the commencement obstinate tenesmus, followed later on by dysenteric diarrhœa. To these are superadded a series of cerebral symptoms: fanciful, discontented temper, giddiness, headache, sleeplessness, all possible eccentric neuralgias, failure of memory, understanding, energy, and will; patients become untrustworthy, and are very regardless of truth, especially when they are questioned about their habit; also paralysis, diseases of the bladder, etc., are apt to set in. I saw, a short time ago, the photograph of a Javanese opium-eater, and I can only confirm Hammer's[1] comparison of the class to "exhumed corpses." Chronic meconismus generally terminates in an early death, yet there are cases recorded of opium-eaters who have pursued the custom for thirty and forty years, and lived to seventy or eighty years of age. Thus the case of a doctor[2] is related, who, for forty-seven

[1] See *Husemann's* Toxikologie. 1862. p. 609.

[2] *Fleming*, Brit. Med. Journ. Feb. 15, 1868.

years, though with intermissions, took large quantities of tincture of opium—one ounce (= 30.0)—daily, and at the same time attended to the duties of a large and laborious practice as accoucheur. To what extent opium-eaters push the habit is proved by their own confessions in ancient[1] and modern[2] times. A woman forty-four years of age took a gallon of tincture of opium monthly, and suffered eventually from sleeplessness and headache, but could not wean herself from the habit. I can state from my own experience how far our morphine injectors go; I know several colleagues who have reached a gramme (15 gr.) of morphine muriate, and even more, per day. Opium-eaters are not, however, secure against acute opium-poisoning, as, *e. g.*, is proved by a case described by Ludlow,[3] in which an opium-eater once took a whole ounce of laudanum instead of his usual half ounce, and very nearly died of it.

Even children can be made opium-eaters, as is seen by the reports from the above-named manufacturing districts. Opium is given to them from their birth, and the dose soon reaches 20 to 25 drops per day, but they look very miserable and die within the first two years of their life of atrophy or hydrocephalus (Grainger).

Morphine injection also exercises an influence on those addicted to it, especially as regards the mind; but they have usually a good appetite, and their digestion on the whole is not disturbed; they drink but little beer and wine, and hardly smoke at all. I have known cases in which persons have had morphine subcutaneously injected every day for ten or fifteen years, without their looking particularly ill.

Opium-smokers do not appear to succumb so rapidly to the effect of chronic meconismus as those who eat or drink opium; at least their appetite does not wholly fail, and the disturbances in defecation are much slighter. Cases are well known of chronic illnesses which require large doses of opium for a long time, often for years, yet the patients do not fall victims to morphis-

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[1] Confessions of an Opium-Eater. *Husemann's* Toxikologie. 596.

[2] *W. Whalley*, Confessions of a Laudanum-Drinker. Lancet. No. 2. 1866. p. 35.

[3] Brit. Med. Journ. July 7. 1866.

mus or meconismus; therefore Macpherson may be partly right in regarding moderate indulgence in opium as innocuous.

Opium-smokers exhibit the same symptoms as opium-eaters, although it is perhaps a question whether the morphine is not decomposed at that high temperature.

Analysis of Symptoms—Mode of Action of Opium and Morphine.

Opium and morphine are substances which act mainly on the nervous centres and upon the nervous system generally. As these differ in different men, and still more so in different classes of animals, experiments on animals can only throw light on the symptoms of poisoning in human beings in so far as the symptoms produced in them agree with those observed in the human subject.

How carefully we must proceed in our deductions from the animal to the human subject with regard to these very poisons, is shown by the circumstance that some animals—pigeons, for instance—can with difficulty be poisoned by morphine; that other animals, *e.g.*, frogs, after opium regularly manifest tetanic symptoms, but not so constantly after morphine; further, that dogs, cats, etc., can often take enormous doses without their producing narcotism or death.

Nevertheless it is from experiments on animals that we obtain the best knowledge of the action of these poisons, and of the sequence of the symptoms.

The influence of morphine upon the heart is seen when poisonous doses are given, and consists, in animals also, in initial acceleration of cardiac contraction, which is succeeded by diminished frequency of pulsation, and ultimately by absolute cessation of cardiac action, the contractions becoming irregular shortly before death. The cause of the initial acceleration of the cardiac action has not yet been sufficiently elucidated by experiments; but it seems very probable, from the researches of Gscheidlen, that the musculo-motor elements in the heart are first stimulated by morphine, for when he had divided the vagus of a dog or rabbit before poisoning with morphine, the frequency of pulsa-

tion increased still more after the poisoning; this experiment seems to support the above conclusion, more especially as the influence of this poison on the sympathetic is comparatively slight. The subsequent retardation of cardiac contractions, however, depends upon an excitement of the vagus at its origin in the brain, for, in the first place, the retardation does not occur when the vagi have been divided before the poisoning; and secondly, the retardation sets in immediately when solution of morphine is injected into the peripheral end of the carotid, therefore in the direct current towards the brain.[1] At the same time, the extremities of the vagus in the heart are thrown into a state of increased excitability; with large doses of morphine, however, the extremities of the vagus become paralyzed; consequently, with very large doses of morphine, the pulse ought eventually to become again more frequent (through paralysis of the vagus); but it is not so, and for this reason, that, as Gscheidlen has shown, morphine exerts eventually a paralyzing action also on other portions of the heart, especially on the excito-motor ganglionic cells in it. But the cardiac muscle also experiences a considerable loss of excitability, and remains motionless when strong currents are brought to bear directly upon it. Therefore, cardiac contraction must always diminish more and more, till it ceases altogether.

Morphine exercises first a constricting, then a dilating influence on the vessels, through the vaso-motor nerves which are primarily excited, and subsequently paralyzed at their centres. Gscheidlen succeeded in directly observing this influence on the vessels in the abdominal cavity of animals; the peripheral portion of the vaso-motor system is affected in the same way even when the influence of the central organ is cut off by division of the cervical marrow. In severe poisoning complete paralysis of the vaso-motor centre takes place, but not complete paralysis of the peripheral vaso-motor nerves, for these can still be stimulated by direct irritation or from the cervical marrow, so as to produce contraction of the vessels.

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[1] *Gscheidlen*, Untersuchungen a. d. physiolog. Laborator. in Würzburg. II. 1. Leipzig. 1869.

The blood-pressure is in accordance with this condition of the heart and its vessels; according to Gscheidlen it rises at the beginning of the action of morphine, and even when the pulse becomes slow this increase of blood-pressure still continues, a circumstance doubtless depending on the vaso-motor contraction of the vessels; subsequently the blood-pressure becomes subnormal, a natural result of the dilatation of the vessels and the diminution of cardiac force. As in human beings, so also in animals, respiration is retarded; this retardation proceeds from diminished excitability of the respiratory centre in the medulla oblongata, as Gscheidlen's experiment proves, in which, upon injection of the poison towards the brain through the peripheral extremity of the carotid, retardation of respiration at once set in. This diminution of the activity of the respiratory centre may lead to complete apnœa, and so to death by asphyxia.

Contraction of the pupils is observed in animals as well as in men; this symptom probably depends on excitement of the oculo-motor nerve.

According to O. Nasse[1] morphine and opium increase intestinal movements, and the intestine is more sensitive under their influence to other excitations. This may account for the effect of opium and morphine in producing tenesmus, and not, as is generally assumed, inactivity of the intestine.

In human subjects some dryness in the throat, though not very considerable, is observed; in dogs violent salivation generally occurs, which depends either upon reflex irritation of the gustatory nerves, or upon the influence of morphine on the calibre of the vessels, or perhaps upon an action upon the secretory filaments.

The peripheral motor nerves, by the direct application of the poison, are at first thrown into a state of excitement, which lasts only a short time (Gscheidlen), and then into the opposite condition of greatly diminished excitability; daily experience teaches us that the sensory nerves and nerve-extremities in the human subject are similarly affected, for when we administer a subcutaneous injection of morphine the nerves lying nearest to the

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[1] Beiträge zur Physiologie der Darmbewegungen. Leipzig. 1866. p. 58.

point of application suffer greater reduction of excitability than others; it is very difficult to demonstrate this in the case of animals.

This influence of the nerves is in itself an obstacle to reflex action, and a considerable impediment to the operation of the will. The influence of morphine upon the cerebrum is very marked, especially on its gray matter, the excitability of which is reduced in a very remarkable manner. Though we find no anatomical changes in the brain to explain this influence, and though most probably the hyperæmia of the brain commonly found is not a primary, but a secondary effect, yet a simple analysis of the symptoms affords evidence that the action of opium determines a change in the excitability and the excitement of the individual ganglionic cells, so that there is at first an increase and later on a diminution of this excitement. If these ganglionic cells come completely under the influence of morphine, no impulse, no expression of the will can be carried into effect; the influence of the brain is to a certain extent eliminated. As to its possible influence on the spinal marrow we have no experimental evidence, but it may be concluded from analogy that the excitability of the spinal marrow is affected in the same manner as that of the rest of the nervous system; it is evident, however, that the influence upon the spinal marrow in the human subject is less marked than that upon the brain.

The convulsions which occasionally come on during morphine-poisoning, and which correspond to opium-tetanus in frogs, might be supposed to proceed from excitement of the spinal marrow at a time when the reflex inhibitory centre, the brain, is already in a condition of diminished excitability. The comparatively rare appearance of this symptom, however, proves that the changes in the two organs proceed almost *pari passu*.

The vomiting, which is so frequent a symptom, must, in most cases, be due to irritation of the vomitory centres by the poison; at any rate, the circumstance that vomiting sometimes occurs after the poison has run its course and convalescence has set in points to a central origin.

The action of the poison upon the urinary bladder is in harmony with its other effects; it first causes irritation of the detru-

sor urinariæ vesicæ with consequent dysuria, later on paralysis of the same muscle, so that in the dead body the urinary bladder is found distended, while there may be dysuria during life.

The most characteristic symptom of chronic opium- and morphine-poisoning is general disturbance of nutrition; this, however, is not the result of increased tissue-degeneration or of accelerated tissue-change, but is due to diminished absorption of food in consequence of the catarrh of the stomach and intestine which exists. This defective nutrition can never give rise to a sensation of hunger, on account of the steady simultaneous reduction of the impressionability of the sensory nerves. The excreta of persons in this condition, though less than in the normal state, are nevertheless in excess of the ingesta; hence the result is complete emaciation. Much has been written upon tissue-change under the influence of morphine and opium, and it has been generally maintained that change of tissue is retarded; Boecker[1] especially maintained that the solid constituents of the urine were diminished under the use of opium. Experiments which I have made with morphine on dogs with the necessary precautions[2] showed that by the use of morphine the decomposition of the nitrogenous tissues suffers a very slight decrease—a result which depends on the diminution of blood-pressure and of the flow of fluids through the parenchymatous tissue. A further investigation carried out by Dr. J. Bauer and myself,[3] as to the excretion of carbonic acid under the influence of morphine in dogs and cats, showed that morphine acts only indirectly upon the excretion of carbonic acid by its influence on muscular activity. When the muscular movements were increased by morphine, or when convulsions in animals were produced, the formation and excretion of carbonic acid were greater than in the normal condition; but if, on the other hand, morphine in-

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[1] Beiträge zur Heilkunde. 1849. Bd. I. und Zeitschrift f. Hygiene von Oesterlen. Bd. I. Heft 1.

[2] Untersuchungen über die Zersetzung des Eiweisses in Thierkörper unter dem Einflusse von Morphium, Chinin und arseniger Säure. München. 1871. und Zeitschrift für Biologie. 1871.

[3] Ueber den Einfluss einiger Arzneimittel auf den Gasaustausch bei Thieren. Zeitschr. f. Biologie. 1874. pp. 336–372.

duced muscular inactivity or sleep, the production and excretion of carbonic acid were diminished. The loss of appetite which chronic opium-poisoning creates may depend somewhat upon the paralytic condition of the vessels and nerves brought about by the constant influence of the poison.

As to the origin of the neuralgias, anæsthesiæ, hyperæsthesiæ, and the other symptoms of chronic meconismus, it is explained partly by the general disturbance of nutrition, which leads to fatty degeneration of most of the structures of the body, partly also by the direct influence of the poison upon the substance of the nerves.

Results of Autopsies.

Characteristic as is the clinical type of opium- and morphine-poisoning, there is very little which is characteristic in the anatomical appearances after poisoning cases have terminated fatally.

We generally find little change in the alimentary tract, and if we discover, in a few cases, hyperæmia of the gastro-intestinal mucous membrane, it is probably due to the antidotes, emetics, etc., employed. On the other hand, we may detect opium in the contents of the stomach by its color and smell.

In the heart we usually find dark, fluid blood, but this also is not constant, for the blood is sometimes found coagulated. Hyperæmia of the brain and its membranes is most constant; sometimes an accumulation of fluid is found in the subarachnoid spaces and in the ventricles; sometimes, also, sanguineous effusions of greater or less extent in different parts of the brain. The condition of the lungs is also by no means constant. According as death has set in rapidly or slowly, we find more or less pulmonary hyperæmia and œdema; we also find, generally, congestion of the liver. The bladder is generally found distended, with urine in which morphine can be detected chemically.

All the other anatomical conditions which have been observed are accidental, and not due to opium-poisoning as such.

Diagnosis and Differential Diagnosis.

Poisoning by opiates may be mistaken for acute alcoholism. The history of the case, the absence of alcoholic odor, the odor of whatever is vomited, the absence of alcohol, and presence of morphine in the urine, may protect us from an error of this nature.

Again, we might confound opium-poisoning with sanguineous apoplexy, or with congestion of the brain, and indeed with all diseases which involve increase of intracranial pressure; the healthy condition of the heart and arteries, the absence of partial paralysis of the facial muscles, the equality of the contracted pupils, may enable us to differentiate between them.

It is often impossible to distinguish opium-poisoning from poisoning by other narcotics, yet chloroform, ether, hydrate of chloral would betray themselves by their smell, while mydriasis would lead to the diagnosis of poisoning by atropine or hyoscyamine. The presence of erectio penis would point to opium.

In children, opium-poisoning may be confounded with acute hydrocephalus, and in fact such mistakes have occurred; when the history of the case is not to be had, we may be guided to a correct conclusion by the absence of a contracted abdomen, by the nature of the matters vomited, and by the equally and strongly contracted pupils.

Prognosis.

In general, the prognosis depends upon the quantity of the poison absorbed into the blood.

An important prognostic sign is the condition of the pupils; the greater the contraction of the pupils, the more grave is the poisoning; if they are contracted to the size of a pin's head, we may regard the case as dangerous.

The prognosis will also depend upon the question, whether vomiting has occurred spontaneously, or only after the use of emetics, also upon whether the stomach-pump was applied early; it will also be influenced by the condition of the patient's strength, and especially by the state of his heart.

During the progress of acute poisoning, the occurrence of per-

spiration is to be regarded as a favorable sign. Jardine Murray[1] mentions that he has observed this in two severe cases of opium- and morphine-poisoning in children.

Treatment of Acute Opium- and Morphine-Poisoning.

If the poison has been taken in by the mouth, our first duty is to empty the stomach of its contents, so as to prevent the absorption of the poison. The sooner the stomach is emptied, the more favorable the result will naturally be. But this is not only necessary at the outset of the case, but also later on, as morphine and opium often remain in the stomach for many hours.

In determining the best method of removing the contents of the stomach, we must be guided chiefly by the length of time which has elapsed since the poison was taken; if it has been taken quite recently, emetics are advisable. The most effectual of these are sulphate of zinc, tartar emetic, ipecacuanha, and sulphate of copper. Still, in many cases, vomiting cannot be induced by these means, because the excitability of the extremities of the sensory nerves in the mucous membrane of the stomach is so greatly reduced by the narcotic poison that no reflex movements can be excited. Tickling the throat also frequently fails to produce vomiting. In such cases we are in the habit of applying mustard poultices to the region of the stomach, of administering infusion of mustard, etc., in order to restore the excitability of the gastric nerves, and thus produce the desired effect. We may, also, as in a case narrated by Moerz, inject apomorphine subcutaneously, in order to excite central vomiting; this often succeeds when emetics administered internally have failed. I once had an opportunity of observing a severe case of morphine-poisoning, in which apomorphine failed to induce vomiting in a patient who was lying in profound sopor, but the collapse, shortly after the injection, became far more decided than before.

Therefore, useful as emetics may be in themselves, we must not forget that, even under the most favorable circumstances,

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[1] Edinburgh Med. Journ. Feb. 1858.

they may decidedly promote and aggravate the collapse which is imminent in consequence of the action of the poison. For this reason it is preferable to empty the stomach by means of the stomach-pump, as it can be used repeatedly, and does not promote collapse.

When emetics can be got to act, they must be administered repeatedly, for it is a matter of frequent experience that even in the third and fourth attack of vomiting, and even later, poison is still found in the matters vomited.

Emetics are attended with another disadvantage; in case of recovery, they may ultimately produce violent gastritis, and certain appearances found upon the mucous membrane of the stomach in autopsies are to be attributed to the irritant action of tartar emetic, etc.

In the next place, we should attempt, as far as possible, to neutralize by the so-called chemical antidotes the poison which has been introduced before it is absorbed. There are no chemical combinations of morphine which are harmless, yet we can produce some combinations not readily soluble; as, for instance, its compound with tannic acid, which is only very slowly soluble in the digestive fluids—according to Taylor, about as slowly as pure morphine; but nevertheless tannate of morphine is by no means innocuous.

It is therefore desirable in practice to combine the administration of emetics with tannin, or, by means of the stomach-pump, to wash out the stomach with fluids containing tannin, *e. g.*, decoction of sage, or an infusion of coffee. A method which is sometimes very valuable in order to prevent complete narcosis is the ambulatory treatment; *i. e.*, the patient, supported by two persons, is constantly walked about for hours together. Once coma has set in, this treatment must be avoided, as it might eventually promote respiratory or cardiac paralysis.

In the case of little children, it is desirable to prevent their falling asleep by moving them about, or by keeping the air surrounding them in agitation; the same effect may be produced by painful stimulation of the skin. If sopor has once set in, we must try, by the administration of stimulants, strong black coffee, ether, etc., to keep off paralysis of the nervous centres. If

respiration and cardiac action begin to be irregular and insufficient, the stimulants must be more frequently administered, and supported by violent cutaneous irritation, cold shower-baths, energetic douches with a full stream, flicking the bare skin with wet towels, etc. If cessation of respiration seems imminent, artificial respiration, either by means of pressure on the thorax or by electric stimulation of the phrenic nerve, may prevent the complete arrest of respiration.

Subcutaneous injections of camphor, ether, etc., may perhaps keep up the excitability of the medulla oblongata and of the heart, till the danger is diminished by the elimination of the poison.

Special mention is due to bleeding and transfusion. Sometimes the symptoms present, especially the cerebral symptoms, may indicate the advisability of venesection ; but it must not be forgotten that very little good is done by slight venesections, as they only remove a very small quantity of the morphine relatively with the blood, the poison being equally diffused through the whole body ; on the other hand, there is the danger, by withdrawing considerable quantities of blood, of reducing the excitability of the respiratory centre and the cardiac muscle, and thus decidedly promoting the onset of acute collapse. Taylor remarks also very pertinently [1] that venesection must necessarily hasten the absorption of the poison still remaining in the stomach.

It will therefore be advisable, in general, to abstain from venesection, all the more because it possesses only a very limited power of arresting possible cerebral hemorrhage. We find how injuriously bleeding may act in opium-poisoning from a case given by Gallaher,[2] in which a lady who had taken two ounces (= 60.0) of laudanum was seized with convulsions after venesection ; as well as from Stafford's case, quoted above, which terminated fatally.

On the other hand, transfusion of blood might have very favorable results, especially if it could be accomplished directly from vessel to vessel, at the same time that a depletory withdrawal of blood was going on, as thus more poison would be eliminated

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[1] Loc. cit. p. 87.

[2] Americ. Journ. April. 1858.

from the body, and the fluid remaining in the body would contain a more diluted, and therefore less injurious, solution of morphine. As far as I know, however, no experimental observations have been made of this mode of treatment, nor has it been tried in practice.

Lastly, we must notice the antagonism said to exist between morphine and atropine.

The antagonism between these two substances, apart from some hints of it in ancient writings, was clearly stated for the first time by Prosper, Albin and Lebel in 1570,[1] and since then it has been repeated from time to time by different authors. Thus Carrignan in 1838, and Graves and Angelo Poma in 1843, repeated the assertion.

Camus[2] was the first to investigate the question experimentally, by poisoning rabbits and sparrows with minimum fatal doses of morphine, and then giving them atropine. Three-quarters of the animals experimentalized upon died; rabbits also died in one and one-third hours after the administration of fifteen grains (1.0) of morphine, notwithstanding the subsequent administration of fifteen (1.0) and four grains (0.25) of atropine; they even died considerably sooner than if morphine alone had been answerable for the fatal result; hence he concluded that the supposed antagonism did not exist. The animals which he selected for experiment are not the most suitable for this purpose, and the doses given are certainly too large; we might also add that Camus introduced the antidote too early, before the morphine had actually begun to work.

Latterly a series of controversial reports have been published for and against the supposed antagonistic effects of atropine in morphine-poisoning;[3] but we cannot draw a decided conclusion from these cases, because either the dose in operation was not known, or the treatment was not purely antagonistic.

[1] *Frommhold*, Ueber den Antagonismus zwischen Opium und Belladonna. Inaug.-Diss. Leipzig. 1869; and *Froehlich*, Historische u. experimentelle Beiträge zur Lehre vom physiolog. Antagonismus der Gifte. Pharmacolog. Untersuchungen von Rossbach. Würzburg. I. Bd. p. 190 ff.

[2] Gaz. hebdomadaire. 11 Août. 1865.

[3] See *Husemann's* Referat in Canstatt's Jahresbericht. 1865. Bd. V. p. 122 ff.

Some light is thrown on this subject by the researches of S. Weir Mitchell, W. W. Keen, and G. R. Morehouse,[1] who, in the U. S. A. Hospital for Injuries and Diseases of the Nervous System, tried experiments with both poisons on sufferers from neuralgia, etc., by means of subcutaneous injection, with all the precautions which are possible in human investigations. They come decidedly to the conclusion that no antagonism exists between these poisons with regard to cardiac contraction, or in their action upon the alimentary canal, but that there is an antagonism between their action on the pupils and, in a certain sense, on the brain; the bladder symptom, dysuria, is aggravated by both poisons.

Erlenmeyer[2] also made experiments on patients, and found that frequency of the pulse is induced by atropine, and not by morphine; that an antagonism may perhaps exist with regard to respiration, and that a marked antagonism exists with regard to the pupils, as Graefe[3] has confirmed. Graefe states that atropine produces paralysis of accommodating power; morphine, on the other hand, causes cramp of the accommodating power, and that the antagonistic action of these two substances affects not only the iris, but also the tensor chorioideæ. Harley[4] is a powerful opponent to the theory of antagonism; he concluded, from experiments on horses and dogs, not only that no general antagonism exists, but that the action of morphine is considerably strengthened by atropine, and that morphine is utterly incapable of restraining the action of atropine.

The fact that atropine dilates the pupils, while morphine contracts them, may have led to the view that the two poisons are antidotes to one another. But even this remarkable action upon the pupils is by no means to be regarded as decidedly one of antagonism. For in animals[5] we can succeed in dilating with atropine a pupil which has been contracted by morphine, whereas

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[1] Hay's Americ. Journ. July. 1865. p. 67 et seq.

[2] Berliner klin. Wochenschrift. No. 2. 1866.

[3] Deutsche Klinik. 16. 1861.

[4] Brit. Med. Journ. 1868. March 8 and April 4. 11.

[5] *Froehlich*, loc. cit. p. 231.

investigators have generally failed to counteract atropine mydriasis with morphine, as ought to be the case in real antagonism.

On the other hand, there are a number of cases reported which seem to intimate that, in the human subject, a real antagonism may exist, at least when small doses are in question. (See Atropine.)

The consideration of the action of both these poisons upon the heart and its contraction is very important.

According to Froelich, minimum fatal doses of morphine muriate, administered to the frog, first increase the number of cardiac pulsations, and then diminish them till death supervenes (from cardiac paralysis); this gradual diminution is not inhibited by small or by fatal doses of atropine; cardiac paralysis appears to set in all the sooner when both poisons are administered simultaneously; but atropine asserts itself so far that it paralyzes the extremities of the vagus; morphine is quite incapable of arresting the paralysis of the vagus and of the heart established by atropine; on the contrary, it would seem as if the combined action of the two poisons aggravated the cardiac paralysis.

It also appears, from the researches of Koning,[1] that the simultaneous action of morphine and atropine gives rise to a combined form of poisoning, in which nothing antagonistic is observable, except with regard to respiration; Koning thinks he has observed that it comes less rapidly to a stop from atropine-poisoning when morphine has been subsequently given; this, however, Froelich denies. Reese[2] also failed to detect any antagonism between the two poisons in experiments on animals; on the contrary, he concludes, from his investigations, that the action of atropine is strengthened by morphine.

From a purely physiological point of view, we are now, as Bezold[3] has defined it in his theses on atropine and morphine,

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[1] Over de antagonistische Wirkung van het Morphium en de Atropine. Arnhem. 1870.

[2] American Journ. N. S. 122. p. 373. April. 1873.

[3] *v. Bezold* and *Bloebaum*, Ueber die Wirkungen des schwefelsauren Atropins. Untersuchungen a. d. phys. Labor. in Würzburg. 1867; *Gscheidlen*, Ueber die physiolog. Wirkungen des essigsauren Morphiums. Untersuchungen a. d. phys. Laborat. in Würzburg. 3. Heft. 1868.

in this position: morphine induces paralysis of all cardiac nerves, of the vaso-motor centre, of the sensory and motor nerves, the paralysis being preceded by a short period of excitement; atropine paralyzes the same parts of the nervous system, without, according to v. Bezold, inducing preceding excitement, or, according to Rossbach, after a brief antecedent excitement. We infer from this that both poisons act in the same manner, and that, though they may appear to be antagonistic in the first stage of their action, as the symptoms of their action differ as to time and intensity, yet finally the action of both poisons is cumulative and all the more surely fatal.

It is only on respiration that their action appears to be antagonistic; at least Gscheidlen asserts that morphine paralyzes the respiratory centre even to the production of apnœa, whereas Bezold states that atropine excites this centre, but adds, that in the early stage of its influence this excitement is slightly checked by the action of the pulmonary portion of the vagus. Erlenmayer also observed as a result of the administration of atropine in human subjects, increased frequency of respiration; he found also that, when both poisons were given, the respiration was not materially altered.

The question, whether there is any antagonism as to their effect upon the brain, is answered in the affirmative by Weir Mitchell, Keen, and Morehouse, who succeeded in neutralizing or at least alleviating the sopor induced by opiates in the human subject, by subcutaneous injection of atropine; in the same way morphine moderated the symptoms of atropine in the human subject. These investigators employed one-thirtieth of a grain of atropine to each one-quarter of a grain of morphine ($1:7\frac{1}{2}$). According to Dodeuil,[1] four parts of morphine are rendered innocuous by one part of atropine. No one will care to try larger doses than these. Murdock[2] witnessed the rapid recovery of a woman who had taken one and a half drachms (= 6.0) of laudanum, upon the subcutaneous injection of one-quarter of a grain (= 0.015) of atropine, two hours later; dilatation of the

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[1] Bull. de Thérapeut. p. 275 ff. 1865.

[2] New York Med. Record. Oct. 343. 1871.

pupils after half an hour; return of consciousness after several hours.

The excitability of the sensory nerves is distinctly reduced by both these poisons, and, according to Erlenmayer, in a greater degree by both combined than by one alone. Neither is there any antagonism with regard to their action on the alimentary canal; morphine fails to diminish the dryness of the throat, which is a constant symptom of atropine-poisoning, and the vomiting which so often follows morphine is not checked by atropine, as all investigators unanimously admit; according to the statements of the Americans, it is increased: so that, for instance, emetics which have been given in cases of morphine-poisoning, do not begin to act till atropine is administered. Both poisons also agree in inducing dysuria.

But although from the physiological point of view we cannot admit an actual antagonism between these substances, and although in experiments on animals no favorable results have been obtained, yet we have a large number of cases reported which show that atropine can be used with advantage in morphine-poisoning.

Although the great majority of clinical reports on this subject are not absolutely clear and conclusive, yet it would, I think, be too sceptical to shut one's eyes entirely to these facts. Still, there is always a difference between a useful remedy and an antidote in a case of poisoning.

If we believe that morphine causes death by reducing the excitability of the respiratory centre to the extent that even excess of carbonic acid in the blood cannot stimulate it to develop the necessary respiratory movements, and that consequently death by morphine is death by carbonic acid, it is not incomprehensible that atropine, by virtue of its influence upon respiration, should partially counteract the effects of morphine. Naturally, if morphine is absorbed in sufficient quantity to cause cardiac paralysis, atropine can be of no avail; we have also to guard against giving atropine in doses which might themselves induce cardiac paralysis, or even in doses which, when combined with morphine, would complete the cardiac paralysis.

It is possible that atropine might, for a time, be as useful as artificial respiration.

We may be allowed to quote a case in point, out of the many.[1]

H. S. Schell[2] relates an attempt at suicide by poisoning, in which a young lady, having taken one and a half ounces (= 45.0) of laudanum, had lain for one and a half hours in deep coma; the stomach-pump and emetics had been tried in vain. Thirty drops of tincture of belladonna were administered internally, then one-forty-eighth of a grain (= 0.00125) of atropine injected subcutaneously, upon which the respiration, which was rapidly failing, and the pulse, which was almost extinct, became again observable. Vomiting followed, and her condition improved; two similar injections were again given; vomiting and improvement again followed; finally, the patient recovered. A case of a man who was poisoned with two ounces (= 60.0) of laudanum is communicated by Thomas Thatcher Graves,[3] in which no vomiting occurred; the doctor, who did not see to the case for two hours, threw into the patient's throat one drachm (= 4.0) of tincture of belladonna, whereupon he almost immediately (!) was so revived that he was able to speak and to take another spoonful of the tincture himself. The pupils became dilated, and after two hours recovery set in.

We may give small quantities of atropine, either in the form of tincture or extract of belladonna, or atropine itself may be given either internally or subcutaneously. Very large doses of atropine have, however, been tolerated in morphine-poisoning, as, among others, Carter's[4] case proves, in which twelve consecutive injections of atropine were made, which altogether contained about three-eighths of a grain (0.025) of the alkaloid. The case ended in recovery; the dose of opium taken was not known.

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[1] *Frommhold*, loc. cit., quotes from medical literature eighteen cases of atropine-poisoning with morphine treatment, and fourteen cases of morphine-poisoning with atropine treatment, which all terminated favorably, although in most cases very large doses had been taken.

[2] Philad. Med. Times. p. 134. 1872.

[3] Boston Med. and Surg. Journ. 1872. 24. Oct.

[4] Philad. Med. Times. May 1. p. 277. 1871.

All authors are agreed that the first effect of atropine is dilatation of the pupils, which often sets in after one-quarter or one-half an hour, but sometimes it does not appear for several hours; this may be due to slower absorption into the circulation so much reduced by the morphine.

The value of the atropine treatment of opium- and morphine-poisoning may perhaps be approximately estimated by the statement of Johnston,[1] that out of seventeen cases of opium-poisoning which he witnessed, eleven recovered under atropine treatment, while six died.

That there are cases which end fatally in spite of atropine treatment, is evident not only by Johnston's cases just quoted, but by a number of other cases on record.[2] In a case communicated by John Ogle,[3] a man fifty-five years of age, who had taken an ounce (= 30.0) of laudanum, died in twenty-seven hours, in spite of the administration of twelve and one-half grains (= 0.75) of extract of belladonna.

Instances are not wanting[4] in which the symptoms of morphine-poisoning were so aggravated by atropine that its use had to be discontinued. These cases, however they may negative a true antagonism in atropine, do not take from it all value as an antidote, and they are quite reconcilable with the physiological facts.

Even very severe cases of poisoning may be cured by simple treatment without the use of atropine, as, among many cases, that of Bergsten[5] proves, in which an apothecary's assistant took six grains (0.4) of morphine acetate, and notwithstanding the most violent symptoms, recovered under treatment with strong coffee, cognac, and the stomach-pump. Chatanion[6] also gives a case in which recovery set in after poisoning by five drachms (twenty grammes) of laudanum, without the use of atropine, although vomiting did not come on till after seven hours. In

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[1] Med. Times. 1872 and 1873.

[2] *Robert Brooks*, Philad. Med. Times. p. 708; and others. 1873.

[3] Med. Times and Gaz. Oct. 3. 1863.

[4] *E. g.*, *Todd*, Americ. Journ. of Med. Sciences. p. 131. 1873.

[5] Upsala Läkarefören Förhandlingen. VII. p. 647. 1872.

[6] Gaz. des Hôpit. 1873. p. 32.

such cases, however, we must guard against a false conclusion, and not take a *post hoc* for a *propter hoc*.

Other remedies have been recommended, such as inhalation of oxygen,[1] subcutaneous injections of whiskey, veratrine,[2] etc., quinine[3] internally, prussic acid[4] internally or in enemata, castor oil.[5]

Treatment of Chronic Opium-Poisoning.

Chronic opium-poisoning, opiophagy, etc., morphioenesis, belongs to the category of diseases which are almost incurable, just because the cause of it is generally not far to seek. The weaning from the use of opium or morphine is a laborious task for the patient, as for the physician, and yet upon it rests the only hope of recovery. If such patients are suddenly deprived of the enjoyment of the drug which is poisoning them, they sink into a miserable condition, the most dangerous symptom of which is collapse. They look ill and emaciated, their eyes are heavy, their respiration is labored, they suffer from dyspnœa, anxiety, cardiac palpitation, frequency of pulse up to 120 in the minute, tendency to perspiration, great irritability, dysuria, pains in all possible nerve-regions, especially in the stomach and intestine, want of appetite, thirst, diarrhœa, absolute sleeplessness. This condition may terminate in death, if the use of the drug is not resumed. Physicians are not agreed as to whether opium ought to be withdrawn suddenly or gradually from such persons. According to my experience, the most effectual plan is to arrest the habit suddenly, with one stroke, if we have to do with tolerably hardy individuals; they are not subject to collapse, especially if a large quantity of wine is given to them. Fleming,[6] who defends this view, advises that these patients should be given

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[1] *Farrington*, Philad. Med. Times. p. 743. 1873.

[2] *Todd*, loc cit.

[3] *Kersch*, Memorabilien. 1. 2.

[4] *Blank*, Rev. de Thérap. méd. chirurg. 17. 1857; and *Shearman*, Med. Times and Gaz. March 7. 1857.

[5] Lancet. 1868. Sept. 2 cases.

[6] Brit. Med. Journ. 1868. Feb. 18.

phosphoric acid and tincture of lupuline in a mixture of 10 : 30, a teaspoonful to be administered every four hours. As an antidote to sleeplessness he recommends, in obstinate cases, tincture of cannabis indica with ether. This so-called stage of reaction may last from four to eight days; gradually the patient begins to eat, and a sensation of great physical and moral comfort is felt.

With weakly individuals, however, the amount of the accustomed dose must be gradually reduced. In the East they mix for this purpose an increasing proportion of wax gradually with the opium, till at last there is more wax than opium in the combined mass; in treating opium-smokers they mix more and more tobacco with it. But it must not be forgotten that with every considerable diminution of the dose the so-called reactionary symptoms set in, although in a modified degree; still, it is the frequent recurrence of these symptoms which induces the patient to fall back into his old habit; therefore this gradual process of weaning must be very slowly carried out. If the object is at last attained, iron and quinine may be given with advantage, the skin should be frequently washed with alcohol or acids, active pedestrian exercise should be taken, etc. A few words as to the weaning from morphine injections. In this case also the suspension of morphine produces very violent reactionary symptoms, which, under some circumstances, may demand the outward application of stimulants or the internal administration of narcotics; it is easier to cure a morphine-eater of his passion than a morphine-injector; frequently our only resource is physical violence; for instance, I know a case in which a young doctor could only be cured of giving himself morphine injections by being actually shut up in a room for more than a week. He resisted like a maniac, scratched at the walls with his nails, wept and shrieked from misery, ate nothing, and was unable to sleep, had diarrhœa, etc. At last, after some days of unmerciful treatment, he began to feel better, to sleep, to eat, etc.; from that time his body rapidly increased in weight, his appearance was fresh and healthy, the misanthropy, which had before been predominant, gave way to a longing for social intercourse, he was able to resume his work, and (a circumstance to which I attach much importance prognostically) he recovered his taste

for tobacco, so that he smoked and drank beer as in the days of health; both these habits he had almost entirely abandoned during the whole period of morphine injection.

I have known men who, once cured, looked upon morphine with horror, and shrank from even the occasional injection of it; while others easily fall back into their old vice, inject morphine into themselves again upon the next occurrence of physical pain or mental excitement, and shortly find themselves in the old condition.

In these cases gradual diminution of the quantity injected sometimes succeeds (especially when the patient is kept unconscious of the diminution), but not always. Some patients feel quite distinctly the withdrawal of a small fraction of a grain (a few milligrammes); gradual weaning involves the danger of easy relapse. Some patients are more easily weaned from the use of morphine by the administration of ammoniated alkalies, bitters, or ethereal substances; thus Taylor[1] relates that Coleridge experienced sensible relief by the use of an ammoniated tincture of valerian.[2]

Changes which Opium and Morphine undergo in the Human Organism.

The opium alkaloids, when absorbed into the blood, naturally pass into all the organs, and may be in part decomposed, but they are to a great extent excreted in an unaltered condition, principally through the urine.

Several of the earlier investigators[3] imagined that they had

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[1] Loc. cit. p. 39.

[2] At the moment when these lines were about to go to press, I received a treatise by Dr. Edward Levinstein, entitled "Die Morphiumsucht," as a reprint from the Berlin. klin. Wochenschrift. 1875. No. 48. In this paper Levinstein defends in general the views which have been developed above, and advocates the sudden withdrawal of morphine, and dwells on an aggravation of the difficulty of carrying out the treatment, *i. e.*, that most sufferers from the passion for morphine, with the very best intentions, deceive their physician by taking morphine secretly.

[3] *Lassaigne*, Annal. de Chim. et de Phys. T. 25. p. 102. 1824.—*Orfila*, Traité de Toxicologie. 1843. p. 21.—*Olivier* and *Mooge*, Journ. de Chim. T. 1. p. 217. 1825. *Stas: Taylor*, On Poisons, translated into German by Seydeler. 3d Vol. p. 77.—*Bouchardat*, Bull. du Thérap. Dec. 1861.—*Lefort*, Journ. de Chimie. T. 11. p. 33.—*Dragendorff*, Beiträge zur gerichtl. Chemie einzelner organischer Gifte. 1872. pp. 129 and 130.

detected morphine in the blood, in the urine, and in the various organs, but afterwards it became evident that the question was not ripe for decision, and that their methods were either inappropriate, or they had not been stated with sufficient clearness, so that Cloëtta[1] ventured to maintain that morphine, etc., could not be detected in the organism, and hence concluded that it was decomposed in the system. Vassal[2] and Flandin[3] had formerly given expression to the same opinion. It has, however, been recently proved, especially by Dragendorff and Kauzmann,[4] that morphine is conveyed out of the organism through the urine in an unaltered condition, even though in all investigations some of the alkaloid is not recovered. This deficit is, however, sufficiently explained by the method of isolating the alkaloid, and it is not necessary to admit an alteration and decomposition of the poison.[5]

Morphine appears in the urine soon after it has been taken, as was shown in an experiment by Dragendorff,[6] who detected it quite clearly in the urine of a cat which had been poisoned with nearly half a grain (0.03) of morphine, and killed two hours afterwards. In another experiment[7] the same quantity (0.03) of morphine was injected subcutaneously into a cat; after fifty-two hours the urine contained no more morphine, whereas in a similar experiment morphine was still found in the urine after thirty-six hours. In the case of a human subject,[8] who had taken one-sixth

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[1] Arch. f. patholog. Anatom. 1866. Bd. 35. p. 369.

[2] Considérations medico-chimiques, etc. p. 97.

[3] Des Poisons. See *Taylor*, by Seydcler. III. Bd. p. 76.

[4] *Dragendorff*, Beiträge, etc. 1872. p. 130 ff.; also *Kauzmann*, Beiträge f. d. gerichtl. chem. Nachweis des Morphins u. Narkotins in thierischen Flüssigkeiten und Geweben. Inaug.-Dissert. Dorpat. 1866.

[5] Perhaps an experiment of Dragendorff's (loc. cit. p. 135) is in favor of a decomposition of a portion of the morphine in the bodies of animals. In the case of a man who had been poisoned with morphine, and died in six and a half hours, a substance was separated from the liver, which, with bismuth potassium iodide, threw down an abundant precipitate, such as is characteristic for most alkaloids, but this substance failed to give the characteristic reactions of morphine; this substance might be regarded as a product of the decomposition of morphine.

[6] Loc. cit. p. 132.

[7] Loc. cit. p. 131.

[8] Loc. cit. p. 136.

of a grain = 0.01) of morphine, morphine was detected in his urine only in the first twelve hours, not later. Other experiments, made on dogs with large doses of morphine by Dragendorff and Kauzmann, show that excretion in urine may last for eighty-four hours.

A small portion of the morphine introduced is apparently excreted in the fæces, especially when it has been taken through the mouth; yet Dragendorff[1] succeeded, even after subcutaneous injections of morphine, in detecting an alkaloid in the fæces, which with sulphuric acid alone gave a violet color. The large intestine of a cat still contained some alkaloid seventy-two hours after the administration of morphine. Whether the morphine found in the large intestine and in the fæces has simply not been absorbed, or whether it has been again excreted into the intestine with the intestinal and glandular fluids, is not distinctly ascertained, though the former hypothesis is highly probable. The absorption of the total quantity of the morphine taken by the mouth is certainly not very rapid; thus, sixteen or eighteen hours after small doses had been administered to a cat, Dragendorff and Kauzmann distinctly detected morphine in the upper part of the small intestine. In a human being who had been poisoned some morphine was found in the small intestine after six and a half hours; some of the poison, though only a small quantity, was found in the stomach from sixteen to eighteen hours after its administration.

That morphine makes its way into the tissues is proved by the frequent detection of it in the various organs. Although its detection in the organs is one of the most difficult of problems, still it has often been accomplished. Dragendorff found morphine in the blood of a cat after only twenty-five minutes, and in the human blood six and a half hours after death from poisoning. Morphine can be detected in the liver whenever the poison has been absorbed from the stomach, and it appears relatively to contain more than the other organs, because much is conveyed through the portal vein; but when morphine has been subcutaneously injected, the liver contains less. In one experiment

[1] Loc. cit. pp. 137, 138.

Dragendorff succeeded in detecting morphine in the liver after only twenty-five minutes; he also found it in the bile of a cat. On the other hand, he failed to find morphine in the brain—which, however, by no means proves its absence in that organ.

Chemical Tests for Morphine.

For the purpose of applying chemical tests, we must examine, in the first place, any portion of the poison that may be left, also the matters vomited; the urine and, if transfusion has been practised, the blood must be examined; in cases which terminate fatally, the blood and the liver especially must be submitted to examination.

If remains of morphine are found, it may be recognized as such by Froehde's or Husemann's tests, or by the chloride of iron test.

Froehde's[1] test depends on the circumstance that when a fresh solution of sodium molybdenate in concentrated sulphuric acid (1–5 milligrammes to each 1 c.cm.) is added to morphine or the ordinary salts of morphine, a beautiful violet color is developed, which subsequently assumes a blue tint, then passes into dirty-green, and finally disappears almost entirely. But Dragendorff[2] states that this reaction, though it is very sensitive, and answers to even $\frac{1}{13000}$ of a grain (one-two-hundredth of a milligramme) of morphine, is not peculiar to it, but belongs also to papaverine, salicin, populin, and phloridzin.

Husemann's[3] test is as follows: a solution of morphine in concentrated sulphuric acid, after it has either stood in the cold for twelve to fifteen hours, or has been heated for a long time to 100° C., or for a short time to 150° C., assumes a pale violet-red color, which, on the addition of somewhat diluted nitric acid or of a few grains of nitre,[4] changes at the point of contact to a

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[1] Archiv Pharmaz. CXXVI. 54.

[2] *Husemann*, Die Pflanzenstoffe. 1871. p. 126.

[3] Die Pflanzenstoffe. 1871. pp. 124 and 125.

[4] Also potassium chlorate in crystals, or chlorine water or solution of sodium hypochlorite, yields the same. If solution of chloride of iron be added to the sulphuric acid solution of morphine, altered by standing or heating, this yields a dark-red zone, with violet or peach-blossom colored edge (*Husemann*).

beautiful violet-blue, which color remains at the margin for a few minutes and then assumes a dark blood-red, which only gradually becomes paler. This test gives a characteristic rose-red color even with $\frac{1}{6600}$ of a grain (one-one-hundredth of a milligramme) of morphine.

For the chloride of iron test we take a neutral solution of ferric chloride, and add it either to solid morphine or to a neutral solution of hydrochlorate or sulphate of morphine, and we thus get a very characteristic rich blue color. This test requires that the substance to be tested should be very pure, and should contain one-six-hundredth of morphine (Dragendorff).

For further tests for morphine, see Husemann, loc. cit., pp. 125 and 126.

If we have to examine the matters vomited, the contents of the stomach and intestine, the blood, the organs, etc., we cannot do better than follow so eminent a toxicologist as Dragendorff, who has modified in various particulars the method of Stas and Erdmann, and von Uslar. He gives the following directions: digest the parts to be examined, previously reduced to small fragments, with diluted (1 : 5) sulphuric acid at 50° C. twice for several hours, and use for every 100 c.cm. of the matters to be examined 10 c.cm. of the said acid. Concentrate the extracts and add magnesia till a weak but evidently acid reaction remains. Then evaporate the whole to the consistency of syrup, and digest the residuum for twenty-four hours at 30° C. with 3–4 times its volume of alcohol, to which some sulphuric acid must be added. Filter, wash the residuum with alcohol, distil off the alcohol from the filtrate, and lastly dilute the residuum with a little water. Filter again, and now shake the fluid two or three times in a warm atmosphere with amylic alcohol. Finally, dissolve out the morphine from the watery solution, which will be found to have become ammoniacal, by amylic alcohol. Evaporate the extracts of amylic alcohol washed with water, and purify the residuum by dissolving in water charged with sulphuric acid, filtering, and renewed shaking of the solution, which has again become ammoniacal, in amylic alcohol.

In testing for morphine in the urine, the urea does not interfere with the qualitative, but it does with the quantitative test

for morphine, as it is very difficult to separate urea from morphine. We must, therefore, in general, remain satisfied with the qualitative test.

When the above method is used for testing for morphine, the alkaloid is obtained in an amorphous condition. In order to crystallize it, which may be important in some cases, Dragendorff and Kauzmann recommend dissolving the amorphous substance which has been obtained in strong alcohol, which must then be evaporated at ordinary temperature, during which process morphine crystals form, generally in colorless, stellar groups of 2–3‴ in diameter. It is best to place the alcoholic solution on a watch-glass, or on a concave lens (Erhardt). If it is a case of opium-poisoning, we must test for morphine in the same way.

Poisoning with Santonin.

Santonin ($C_{15}H_{18}O_3$) is the active constituent of santonica (Levant wormseed : Artemisia Contra) ; it behaves towards bases as an acid, so that it is also named santonic acid. Santonin forms colorless glossy foliaceous crystals, which belong to the orthorhomboidal system. It is sparingly soluble in water, more readily so in alcohol, has an alkaline reaction, and a very bitter taste; the crystals assume a yellow color in the light; at the same time the santonin becomes altered and is partially converted into formic acid. Santonin dissolves with a red color in sulphuric acid; its compound with potassium is also red.

Etiology.

Santonin and santonica are drugs very frequently used, and are often employed without medical prescription, and so commonly cause poisoning of a more or less violent character. We have had a considerable number of such cases reported recently; they have generally occurred from taking excessive medicinal doses, and in some cases have ended fatally. Several Swiss phy-

sicians,[1] for example, have published reports which show that santonin readily produces symptoms of poisoning, and Dr. Grimm relates the death of a child, four and a half years of age, with most characteristic symptoms, from six doses of nine-tenths of a grain (0.06) each, administered every three hours. Other cases, some slight, some severe, with very remarkable symptoms, are reported by Dr. Schmidt at Pösneck,[2] Heydloff[3] at the same place, Lohrmann[4] (a very severe case); Snijders[5] describes two cases of poisoning (not fatal ones) from santonin lozenges; the first was that of a child who had taken six grains (= 0.36) of santonin, the second was that of an adult, who had been poisoned by four grains (= 0.25). Linstow[6] has quite recently reported a case deserving of notice: here a girl ten years of age had received about two drachms and a half (10.0) of santonica from her mother, became ill shortly after with violent vomiting and convulsions, and died in forty-eight hours. Many other cases might be quoted. In answer to the question, what is a poisonous dose? it must be noticed, that often very small doses, *e. g.*, two and a quarter grains (0.15) are sufficient to produce symptoms of poisoning, but that only very large doses prove fatal; only very young children, as Grimm's case, mentioned above, proves, can be killed by moderate doses (five and a half grains, equal to 0.36). The German Pharmacopœia fixes as maximum dose 0.1 (one grain and a half) per dose, and 0.5 (seven and a half grains) per day.

Symptoms and Course.

The first symptom which appears after taking santonin or its soda-salt, or santonica, is generally a change in color sense. Hufeland had observed, as early as 1806, that yellow vision was

[1] Schweizer Zeitschrift. Heft 4. p. 492. 1852.

[2] Eigenthümliche Intoxicationssymptome nach dem Gebrauche von Semin. Santonic. Deutsche Klinik. 1852. No. 53

[3] Merkwürdige Wirkung des Wurmsamens. Preuss. Vereinszeitg. No 7. p. 34. 1852.

[4] Würtemberg. Corr.-Blatt. 3. 1860.

[5] Nederlansch Tijdschrift. I. 68. 1868.

[6] Eulenberg's Vierteljahrschr. f. ger. Med. XXI. 80, 81; and Centralblatt f. d. med Wiss. No. 19. 1875.

a symptom of santonin-poisoning; since that time these changes have been frequently observed. Yellow vision is the prevailing symptom of this kind. Spencer Wells[1] observed green vision after the administration of nearly four grains (0.25) of santonin. Heydloff (loc. cit.) has published very interesting communications on this subject. At Pösneck, in Prussia, it was the custom for young and old to take "worm seed" on the 25th of January every year. On one occasion a dyer's family took a considerable number of worm seed, whereupon the whole family took red for orange and blue for green. Schmidt, who also had opportunity of making observations at Pösneck, saw a man and his son who suddenly saw everything green; crimson appeared to them fawn-color, madder-red they took for bronze-color, white appeared to them yellow. Arnet[2] observed this yellow vision disappear again after a few hours. According to the reports of de Martini,[3] the color seen depended, in some cases, upon the quantity of poison taken. After five grains (= 0.3) a patient is said to have had yellow vision; after twice that quantity, first orange and then yellow. This colored sight, according to Farquharson's[4] investigations, set in twenty-five minutes after the introduction of nearly five grains (0.3); it lasts, in general, only a short time, never more than twenty-four hours; in some cases it is intermittent (de Martini).

All authors agree that the urine is affected by santonin. It is increased in quantity and colored yellow; there is frequent desire to pass water, and the increased amount which is excreted is said to contain more solid constituents, especially urea, than in the natural condition; but this still needs confirmation.

As santonin is used mostly in children's cases, who cannot give so clear an account of their color-impressions, it follows that these symptoms are not observed so often in children as in adults. Very careful observers have noticed that violet vision has preceded the yellow vision for a short time. In many, indeed

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[1] Remarks on Santonine, its Properties as a Vermifuge, etc. London Med. Gaz. June. 1848.

[2] Würtemberg. Med. Corr.-Blatt. No. 10. 1853.

[3] Gaz. des Hôp. 34. 1860.

[4] Experiments on Santonine. Brit Med. Journ. Oct. 21. 1871.

in most poisoning cases, this impression of color is the only observable symptom of the poison. But other symptoms involving the brain are not uncommon. Giddiness and headache often occur, with general uneasiness; nausea and vomiting are not infrequently observed. In severe cases, however, trembling of the whole body, actual convulsions, and trismus set in. The face becomes pallid, profuse perspiration covers the skin, the pupils may be dilated, cardiac pulsation and respiration are accelerated, the sensorium is affected even to complete loss of consciousness. The initial restlessness gives place to complete apathy, with sopor, accompanied with involuntary evacuation of the bowels and bladder, and, if collapse comes on, death may supervene in a few hours. These symptoms have been observed by Dr. Grimm in a fatal case, and by Lohrmann in a severe case, of poisoning. In Lohrmann's case, a child three and a half years of age had taken, within an hour, five santonin lozenges (in all, equal to about two and a half grains (0.15) of santonin), and, after a quarter of an hour, had violent convulsions; after three-quarters of an hour the child was unconscious, saw things blue, the pupils were widely dilated and insensitive to light. There was foaming at the mouth, and convulsive muscular twitchings were observed in the arms and legs; the eyes were distorted, the mouth was firmly closed. Consciousness did not return till after three hours; then the convulsions ceased, and the child was quite well the following day.

Urticaria is an occasional but rare symptom; in the case reported by Sieveking [1] of a girl five years of age, who had taken three grains of santonin, it covered the whole body; there was also considerable œdema of the face; both disappeared after an hour. Betz [2] observed several times that the evacuations from the bowels were red, and apparently sanguineous, but they contained no blood-corpuscles. Daniel [3] asserts that he has frequently found blood in the abundant urine.

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[1] On Santonine as a Cause of Urticaria. Brit. Med. Journ. Feb. 18. p. 166. 1871.

[2] Memorabilien aus der Praxis. V. 2. 1860.

[3] On Irritation of the Urinary Organs, produced by Santonica and Santonin. New Orleans Journ. of Med. April. 1869. p. 241.

Analysis of Symptoms—Mode of Action of the Poison.

The chief effect of santonin is no doubt upon the nervous centres; at first their excitability is increased, later on it is diminished. The headache, giddiness, convulsions, and sopor are to be referred to this action; the vomiting which sometimes occurs must be regarded as cerebral, dependent on the effect of santonin on the brain. The changes in the circulation and respiration are also most probably due to the effect of the poison on the nervous centres. The convulsions, which in experiments on animals affect the respiratory muscles, and which also, as van Hasselt and Rienderhoff[1] have observed in their experiments on dogs and rabbits, affect the muscles of the larynx and epiglottis, indicate that death by santonin is in some cases due to asphyxia, of a like kind to that which occurs in poisoning by strychnine. It is clear that the convulsions which in animals invariably precede death are independent of carbonic acid poisoning, and arise from central irritation, because in frogs convulsions after the administration of santonin also occur. Hallucinations are frequently present in poisoning by santonin; according to Rose's[2] researches, they appear in a third of all cases, and may affect all the senses with the exception of hearing. Colored vision, the most remarkable symptom in santonin-poisoning, was formerly traced to different causes. Zimmermann[3] thought that yellow vision was due to yellow coloring of the serum in the blood by santonin. But he soon convinced himself[4] that the blood-serum of a young man, whom he had bled after producing yellow vision by eight grains (= 0.5) of santonin, was not in the least colored yellow, although the remarkably bright-red color of the blood had led him to expect that the serum would be yellow.

Later on, it was supposed[5] that the transparent media of the eye were colored yellow by santonin. But Zimmermann (loc.

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[1] Arch. für holländische Beiträge II. 3. 1860.

[2] Virch. Arch. 1863. XXVIII. 1. 2.

[3] Ueber eine eigenthümliche Wirkung der Santonins. Deutsche Klinik. 1853. No. 16.

[4] Ueber das Gelb- und Grünsehen nach dem Santoningebrauch. Deutsche Klinik. 1855. No. 14.

[5] *F. L. Phipson*, Compt. rend. T. 48. No. 12. 1859.

cit.) failed to see any yellow fluid in the eye, and Rose[1] failed equally to observe with the ophthalmoscope any yellow coloring of the posterior part of the eye. Another supposition was that jaundice was rapidly developed and as rapidly disappeared, and the bile in the blood was supposed to stain the retina and the fluids of the eyes so as to produce yellow vision. But Rose never succeeded in detecting the coloring matter of bile in the blood in such cases. It appears, from the beautiful experiments of Rose, that yellow vision often precedes (as, indeed, even death may) the yellow coloring of the urine, so that santonin causes such changes in the optic nerve and its terminal expansion that the peripheral elements of the retina have lost their normal capability of perception. Rose regards yellow vision as a symptom of santonin narcosis, equally with the headache, sleepiness, hallucinations, etc. Rose made experiments on the spectrum with persons poisoned by santonin, and found that the spectrum, so far as it was seen at all, was seen normally, but that the spectrum appeared shortened. The violet part appeared at first colorless and then black, so that there is a distinct violet-blindness in santonin-poisoning. The organs which perceive the violet rays are therefore excited in the early action of santonin; hence the short, transient violet vision, which is clearly developed especially against dark objects; then subsequently those organs are paralyzed—violet-blindness. How this violet-blindness is produced, whether it is a direct influence of santonin on the violet-perceiving organ, as Helmholtz[2] and Huefner[3] suppose, or whether the retina itself is colored yellow by santonin, as M. Schultze[4] thinks, cannot at present be clearly explained. The former view is, however, the most probable one, especially as Rose's observation that violet vision precedes yellow vision is well grounded and has not been disproved.[5]

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[1] Virch. Arch. XVIII. 1. 2. pp. 15–33. 1860.

[2] Handbuch der physiologischen Optik. Leipzig. 1867. 847.

[3] Archiv für Ophthalmologie. XIII. 309.

[4] Ueber den gelben Fleck der Retina, seinen Einfluss auf normales Sehen u. auf Farbenblindheit. Vortrag. Bonn. 1866.

[5] See *Husemann*, Experimentelle Toxikologie. p. 383. Berlin. 1874.

Results of Autopsies.

Although mild forms of poisoning with santonin are very frequent, cases which terminate fatally are very rare, and I have no knowledge of any satisfactory reports of autopsies. The reports of van Hasselt and Riienderhoff (loc. cit.) show that in animals which have been killed by santonin the evidences of death by simple asphyxia may be expected, *e. g.*, hyperæmia of the lungs, the brain, and the spinal marrow, especially the membranes of those organs, and an engorged heart. No characteristic appearances have been observed. The possible discovery of remains of the worm seeds or crystals of santonin in the stomach or alimentary canal, may under some circumstances lead to a diagnosis.

Diagnosis and Differential Diagnosis.

The diagnosis of santonin-poisoning is very easy if we are acquainted with the history of the case, or if any santonica seeds are found in the excreta; if these data are absent it may be difficult. Santonin-poisoning may be mistaken for congestion of the brain, for meningitis, as well as for poisoning by other substances, especially narcotics. In the case of adults colored vision may supply a basis; but with children this basis can seldom be secured. The examination of the urine is important for fixing the diagnosis. It usually appears of a dark saffron yellow, *i. e.*, when it has an acid reaction. If, on the contrary, it has become alkaline, it is crimson. The saffron-colored urine becomes crimson on the addition of caustic potash, while the tests for the coloring material of gall-nuts and for gallic acid yield negative results.

Prognosis.

As we have already said, santonin-poisoning very rarely proves fatal; the prognosis, therefore, is generally very favorable, both as regards the preservation of life and the complete restoration of health. In medical practice the prognosis is chiefly

dependent on the quantity of poison which has been introduced, also upon the degree of violence of the collapse and the convulsions.

Treatment.

The treatment of santonin-poisoning consists first in the administration of emetics, and afterwards, if santonica has been taken, we must give aperients. No chemical antidotes are known. When once the symptoms of santonin are developed, we must attend especially to the state of the heart and respiration. In case of collapse we must give alcoholic and other so-called stimulants, and if convulsions ultimately come on, we must have recourse to artificial respiration. Ordinary medical considerations will indicate, according to circumstances, when stimulation of the skin, warm baths and even opiates, cold compresses to the burning head, etc., may be needed. Bleeding ought to be entirely avoided.

Changes which Santonin undergoes in the Organism.

Santonin is absorbed from any surface to which it is applied, and enters the fluids of the body. But the absorption of pure santonin from the stomach is not so rapid as that of sodium santonate. A portion of the santonin taken passes away in the fæces, as Rose has shown; he himself found it in a crystalline form in the fæces. The portion which passes into the blood very probably unites with alkalies and forms salts, and these are apparently excreted unchanged in the urine. As mentioned above, santonin is decomposed under the influence of light, and becomes yellow; there is also a yellow pigment found in the urine, which must be traced to santonin. Manns and Falck[1] have called this pigment xanthopsin, and to it they attribute the yellow vision; the names photosantonin or photosantonic acid are better. It is probably this pigment which gives to the urine its yellow, and when alkaline its red color. This coloring

[1] *Falck*, Deutsche Klinik. 27. 28. 1860; and *Manns*, Dissertation, Das Santonin, eine pharmacologische Monographie. Marburg. 1858.

matter may sometimes be found also in the fæces, and when they are alkaline, it dyes them crimson or blood-red, which accounts for the observation of Betz quoted above. Krauss,[1] who occupied himself chiefly with the action of sodium santonate, when he had introduced santonin, found the urine, after an hour, colored yellow; when he had given sodium santonate, after half an hour. This yellow color of the urine may last as long as sixty hours (Falck). The excretion of santonin is not, therefore, in general a very rapid process.

Chemical Test.

The chemical test, which, as far as my knowledge goes, has never yet been demanded in evidence, would have to rest chiefly on the above-mentioned changes in the urine, and on the probable discovery of santonica or santonin crystals in the alimentary canal. It must, however, be remarked that Krauss never succeeded in finding santonin crystals in the intestine. We have as yet no satisfactory method for the separation of santonin from organic substances.

Poisoning with Ergot.

There is no longer any doubt that ergot of rye is a fungus, the Claviceps purpurea, which, springing from the ovary of different graminiæ, chiefly rye, develops spontaneously, especially in wet summers, and appears abundantly upon the ears of rye, etc. But this ergot appears not upon rye only; it is found in rainy summers in great abundance upon wheat, barley, rice, millet, brome-grass, etc. The ergot contains different constituents, which for the greater part have not yet been obtained in an isolated condition. It contains, above all, a fatty oil, which is inert in its pure condition, also a resin and trimethylamine (Walz), and two other substances, which may perhaps be called alkaloids,

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[1] Ueber d. Wirkungen d. Santonins u. d. Santoninnatrons. Tübingen. 1869.

ergotine and ecboline. These two substances are amorphous, of a brown color, and a slightly bitter taste, are readily soluble in water and alcohol, insoluble in ether and chloroform, and have an alkaline reaction. Their salts are always amorphous.[1] Under the name of ergotine we find two preparations, one prepared by Wiggers, the other by Bonjean. Wiggers's ergotine is obtained by freeing the powdered ergot from wax and fat by extraction with ether, then heating with alcohol, and treating the evaporated residuum with water. It consists of a reddish-brown acrid and bitter powder, which is sparingly soluble in alcohol, and quite insoluble in water and ether. It is an impure substance. Bonjean's ergotine is obtained by treating the watery extract of ergot with alcohol, and evaporating off the latter. It is also a reddish-brown powder with an acrid and bitter taste, very readily soluble in water and alcohol. But this ergotine also is by no means a pure substance, but a mixture of several substances. Both, however, act as medicines and poisons, as does the resin above-mentioned.

Ecboline was first obtained by Wenzell from the watery extract of ergot; it is a base which displays very obvious poisonous qualities. It is not yet decisively proved whether these substances are the really active constituents of ergot. Quite recently it has been maintained that the active principle of ergot is a substance which has not yet been isolated, which is soluble in water, but not in absolute alcohol, and has an acid reaction, so that it is to be regarded as an acid.[2] This view, first expressed by Wernich,[3] has been lately supported by Zweifel,[4] who has published a paper on this subject. Therefore a treatise on practical toxicology must limit itself to considering ergot as a whole.

Ergot does not always contain the same amount of active ingredients. It is much less poisonous in an unripe than in a

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[1] *Husemann*, Pflanzenstoffe. p. 521.

[2] Such a body has now been isolated by Dragendorff and Podwissotzky, of Dorpat, and named "sclerotic acid." It is said to possess in high degree the specific virtues of ergot."—E. C.

[3] Einige Versuchsreihen über das Mutterkorn. Berlin. 1874. p. 50.

[4] Archiv für experimentelle Pathologie und Pharmacologie. Bd. IV. p. 407. 1875.

ripe condition; it is most active when it is collected from the ears in the corn-field; if it is kept closely shut up for some time, its activity increases. But if it is kept in open or ill-closed vessels, so that air finds entrance, it gradually loses its activity; also when worked up into bread it becomes decidedly less active.

Poisonings with ergot present different symptoms under different circumstances, so that it is necessary to consider these separate forms of poisoning as distinct from one another. Especially the symptoms which are produced by single large doses of ergot, acute ergot-poisoning, must be distinguished from those which arise from the long-continued introduction of it, and which fall under the head of chronic ergot-poisoning. Lastly, the symptoms which indicate chronic ergotism must be treated under two distinct heads, as the symptoms differ in the most essential points.

Acute Ergot-Poisoning.

Etiology.

Acute ergotism is developed when large quantities of ergot or its preparations are introduced into the human organism. This poisoning is, on the whole, rare, and chiefly affects pregnant women who take the drug to produce abortion; or it proceeds from the administration of overdoses of the poison by medical practitioners—medicinal poisoning. The usual dose of ergot as a medicine is fifteen grains (1.0) repeated two or three times at short intervals; of the watery extract (Ergotinum, Bonjean), which is the preparation most commonly employed in medicine, except the drug itself, single doses of from a grain and a half to eight grains (0.1 to 0.5) are the general rule. These doses, even when administered repeatedly, are by no means poisonous. It is not yet possible to specify the doses which are sufficient to produce ergot-poisoning. At any rate, very large doses are needed to bring about a fatal result, and when death really supervenes, the question is still open, whether, as is frequently the case with pregnant women, other causes, hemorrhage, etc., may not have co-

operated. Thus Richter[1] relates a case of poisoning with ergot, affecting a pregnant woman, in whom it produced abortion, and she died with continued hemorrhage. In this case hemorrhage seems to have been the actual cause of death; at least the consideration of the symptoms observed scarcely admits of any other conclusion.

Symptoms of Acute Ergot-Poisoning.

The symptoms most frequently observed are connected with the stomach, the alimentary canal and its appendages. Eructation, retching, nausea, tendency to vomit, and actual vomiting with simultaneous increase of salivary secretion, sometimes also colic and diarrhœa, are the first symptoms of acute ergotism, and may be produced sometimes by even moderate doses; I myself have witnessed such a case after the administration of twenty-two grains (1.5) of ergot.[2] Individual constitutions must also be taken into account; whereas, with the majority of people, the dose mentioned may fail to produce the symptoms above enumerated, yet in particular cases, especially when there are disturbances in the alimentary canal, these symptoms may be developed in a remarkable manner. Other symptoms are superadded to these which point to an affection of the brain: giddiness, mistiness of vision, headache, and alterations of the pupils, which are generally dilated, but sometimes contracted. Great muscular exhaustion, dejection, and weariness are additional symptoms. Cardiac contraction is also considerably affected by ergot; the principal effect is diminution of the frequency of the heart-stroke, which is sometimes very marked. Thus Bailly[3] found the pulse sink to 64 beats in the minute; Arnal[4] states that four and a half grains of the watery extract (0.3) reduced the pulse from 84 to 60 beats. This retardation of the pulse is the

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[1] Casper's Vierteljahrschrift für gerichtliehe Medicin. XX. 2. 1861.

[2] See also *Dr. Heimann Gross's* experiments, Beiträge zur genaueren Kenntniss der Wirkung des Mutterkorns. Preuss. Vereinszeitung. Nos. 11, 12, 13. 1845.

[3] Ergot et Ergotine. Aet. physiolog. et propriét. thérapeutiq. Bull. général de Thérap. Mai 30. Juin 15. 30. pp. 433, 481, 529, etc. 1870.

[4] Bullet. de Thérapeutique. Juin. 1849.

more remarkable, the more frequent it was before the poisoning; thus Sée[1] observed a reduction of the pulse by 36 beats, and yet could not bring it lower than 64 in the minute. Nickel[2] also mentions that he saw the pulse sink by 20 to 24 beats. This retardation of the heart-stroke, as Gibbon[3] asserts, reaches its climax about half an hour after the ergot has been introduced. In more severe cases stupefaction, sopor, and retention of urine set in, and with the continuance and aggravation of these symptoms death may supervene, all the more surely because not only the frequency of pulsation, but the general action of the heart, is reduced. All investigators are agreed that the arteries are less filled, and become lax and easily compressible. Dyspnœa, etc., follows upon this diminution of the decarbonizing of the blood, and may easily cause death, though a fatal result is among the exceptions. More rarely neuralgic pains are observed in different organs, especially in the fingers, and in the skin, where the nervous affection takes the form of intolerable irritation. In some cases the muscular weakness may continue some days after the poisoning; also actual aberration of intellect is said to have occurred after ergot-poisoning.

If the poison has been taken by pregnant women with the intention of producing abortion, they sometimes attain their object, especially if the pregnancy is far advanced; in the earlier months ergot fails to produce this effect. The character of the symptoms of ergot-poisoning may be more or less modified by the occurrence of the premature birth. The course of the symptoms produced by ergot is generally tolerably rapid.

Analysis of Symptoms—Character of Acute Ergot-Poisoning.

The most evident symptoms in the early stage of the action of ergot-poisoning—retching, vomiting, diarrhœa, and salivary

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[1] Recherches sur les propriétés du seigle ergoté et de ses principes constituants. Gaz. méd. de Paris. Nos. 31–33. 1846.

[2] Beiträge zur Pharmacodynamik. Bayr. Corr.-Blatt. No. 44. 1860.

[3] The Sedative Powers of Ergot. Amer. Journ. of Med. Sciences. Jan. 1844.

secretion—are consequences of the action of the poison on the sensory nerves of the mucous membrane of the alimentary canal; these are excited by the poison, and the excitement is communicated to motor and secretory regions—reflex action.

This explanation avails at least for these symptoms when they set in soon after the introduction of the poison.

The vomiting which sometimes occurs in the later course of the poisoning is, perhaps, traceable to an action of the poison on the central nervous system; in the same way the subsequent diarrhœa is dependent on the influence of the poison on the vessels and the distribution of blood. We have no accurate knowledge as to the origin of the flow of saliva. In all probability it is to be regarded as a reflex salivation, as it follows upon eating acrid substances, and precedes vomiting. The vomiting, dependent on the same cause, is connected with the early stage of muscular weakness. The muscular exhaustion continuing for a longer time is on its side produced by the changes effected in the circulation by the poison. We can only suggest hypothetical explanations of the action of this poison on the brain; we possess no certain knowledge on the subject; only this much may be said with some confidence, that here also the alteration in the circulation may exert a considerable influence. The chief effect of ergot and its preparations is over the organs of circulation, the heart and the blood-vessels. The diminution of cardiac pulsations, and general lowering of cardiac action, possess the first claim to our consideration. The statements of Felix von Willebrand of Helsingfors[1] are very noteworthy, to the effect that the healthy or even the hypertrophied heart contracts under the influence of ergot, so that this diminution of volume may be clearly diagnosed by percussion when the poison has ceased to act; this contraction is naturally followed by a dilatation till the *status quo ante* is reached. With regard to experiments on animals, all investigators agree that with them, as with the human subject, a diminution of the frequency of the heart-

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[6] Notisblad för Läkare och Pharm. 1858. Nos. 10 and 11; *Schmidt's* Jahrb. Bd. 108 p. 299; *Rossbach's* pharmac. Untersuchungen. I. Bd. p. 116.

stroke is produced by ergot and its different preparations. See Haudelin, Briesemann,[1] Eberty,[2] Rossbach,[3] and others.

Eberty brought the frog's heart to a stand-still in diastole by injection of large doses of ergotine into the gastric vein; he traces this effect to irritation of the extremities of the vagus. Rossbach observed some very remarkable movements in his experiments with different preparations of ergot on the hearts of frogs. The pulsations of the ventricle diminished in frequency, those of the auricles remained steady; the filling of the ventricle was incomplete, the contraction of the separate fibres of the cardiac muscles not simultaneous, but alternating, so that frequently a sort of peristaltic movement in the heart was observable; certain bundles of muscles remained for a long time in a state of contraction, while neighboring groups were relaxed. These and similar movements were observed by Wernich[4] also. Rossbach traces this action of the preparations of ergot (he used Wiggers's ergotine, and Wenzell's ecboline) to an influence exercised by them upon the cardiac muscular apparatus, which, as a peculiarly constructed muscle, may even in a physiological sense be regarded as other than a common striped muscle. It is certain that we are not greatly assisted in our attempts to explain the action of ergot on the heart by supposing it to act on the cardiac nerves. Wernich, on the other hand, traces the changes in cardiac contraction not to direct influence of the poison upon the heart, but regards them as secondary symptoms, dependent on the action of ergot and its derivatives upon the vascular system.

The chief effect of ergot is certainly upon the vascular system.

It is a fact that the arteries are contracted; these changes may be somewhat considerable, so that vessels of rather large dimensions appear as very narrow ones with thick walls. This

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[1] Microskop. Untersuchungen über die Wirkung des Digitalin, Veratrin, und Ergotin auf die Circulation. Dissert. Rostock. 1869.

[2] Ueber die Wirkung des Mutterkorns auf die Herzthätigkeit und den Blutdruck. Dissert. Halle. 1873.

[3] Pharmacologische Untersuchungen. Bd. I. p. 214 ff.

[4] Einige Versuchsreihen über das Mutterkorn. Berlin. 1874; and Virch. Arch. Bd. LXI. 505.

contraction chiefly affects the small arteries, but even in the larger ones it is clearly recognizable. On the other hand, there is a dilatation of the veins. The condition necessarily attending these changes is a diminished quantity of blood in the contracted arterial system, and a corresponding increase in the contents of the veins. This fact may be directly observed in frogs as well as in rabbits, and was observed by Wernich not long ago with the microscope in the web of the frog, and was drawn by Holmes by means of the camera lucida, and micrometrically measured by Briesemann.[1]

Clinical experience of the action of ergot in lowering the circulation of the blood entirely corresponds with this. This lowering action is an indisputable fact for the practical physician who has employed this drug, even though the direct experiments made on animals have been questioned from various quarters. The main question connected with this circumstance is how this vascular contraction of the arteries is brought about. It was formerly assumed that ergot caused contraction of the arterial vessels by stimulating their muscular coat, so that they were in a state of active contraction. This contraction of the arteries was then further traced to an influence which ergot was supposed to exercise upon the vaso-motor centre. A true cramp of the arteries was therefore regarded as the effect of ergotine, a cramp that under some circumstances might last long. A considerable shock has been given to this view of ergotine action, universally prevalent till quite lately, from the circumstance that the increase of blood-pressure to be postulated *a priori* from so strong a contraction of the arteries has not been found by any of the later investigators, except Eberty, in their experiments on blood-pressure with the kymographion. Thus Holmes,[2] Haudelin, Hermann, and Wernich found almost constantly a more or less considerable decrease of blood-pressure. The diminution of blood-pressure directly contradicts an active contraction of the arterial vascular system; again, as Wernich shows, such a contraction is disproved by the beneficial influence on arterial aneurisms,

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[1] Dissert.-inaug. Rostock. 1869.

[2] Effets de l'ergot du seigle. Arch. de Phys. 1870. III.

which Langenbeck, Hermanides, and others produced by ergotine injections; lastly, it is opposed by Willebrand's observations, mentioned above, with regard to the diminution of volume of the heart. The question which must next arise is: How, then, is arterial contraction induced? If it is not active, it must be passive. The heart must in a given space of time pump less blood into the periphery than in its natural condition, because less blood is conveyed to it by the systemic and pulmonary veins; there must be an unwonted accumulation of blood in the veins. Such an accumulation of blood in the veins is only possible by a diminution of the tone of the veins, as Wernich insists. This dilatation of the veins, this increased amount of blood in them, can be directly proved. According to Wernich's observations, it is the veins of the mesentery, of the uterus, of the bladder, of the abdominal veins generally, which show most clearly this engorgement after the introduction of ergotine. Wernich draws a parallel between the symptoms of ergotine-poisoning in frogs and those which Goltz has observed in his experiments on pulsation with regard to the circulation. In both cases there is a strongly marked arterial anæmia, and an equally striking venous hyperæmia; in both cases there is a diminution of cardiac contraction leading to entire cessation of cardiac action; in both cases Wernich sees in the dilatation of the veins the primary, in the contraction of the arteries and in the action of the heart the secondary symptom; the arteries, therefore, collapse from want of sufficient quantity of blood, the action of the heart proceeds more slowly or ceases altogether from diminution or entire cessation of the supply of blood to it; so that the action of ergotine appears to lead to an accumulation of blood in the veins. The cause of this decrease of the tone in the smooth muscles of the veins has not been experimentally established with sufficient accuracy. It should be mentioned that Zweifel, in the treatise above quoted, comes to the conclusion, from careful experiments, that not only ergot and its preparations, but a whole series of substances, produced arterial contraction, and that all these substances have one property in common, that of producing considerable pain when subcutaneously injected. He therefore regards the action of ergot on the vessels as by no means its chief action,

but believes that to consist in its influence upon the central nervous system.

A few words will be sufficient as to the influence so often maintained and so often denied of ergot of rye on the action of the uterus, as changes in this organ are not among the most important symptoms in acute poisonings. For the accoucheur the fact is established that ergot may increase pangs already existing, although many maintain that it cannot originate them. Yet it has been proved by various investigators, especially recently by Schlesinger and by Wernich, that even in the unimpregnated uterus of animals, movements take place under the influence of preparations containing ergotine. But these movements, according to our present experience, as they respond to the physiological experiments of the investigators above-mentioned, may be regarded, not as primary effects of the poison, but as secondary and dependent on the arterial anæmia produced by ergotine, etc. Wernich's experiments appear to me here again to be valuable; according to them, in experiments on animals, as a rule, the change of the calibre of the vessels does not influence the discoloration and blanching of the uterus till first movements of the uterus have been observed, of short duration and moderate intensity, but still so evident, that there is no doubt of their existence. It is therefore sufficiently clear that it is not the arterial anæmia or venous hyperæmia alone which causes these movements. On the contrary, it might almost be assumed that the influence of ergot upon the movements of the uterus proceeds solely from an influence of the poison upon the nerve-centres of these movements in the lumbar region of the cord and in its higher-situated parts, as well as in the brain. But even in this case some influence might be attributed to anæmia, induced by the ergot; only when we come to further reflect on the action of the poison on the spinal cord, the hypothesis of a direct action of the poison is much more simple, although the whole question appears as yet to be far from settled in one direction or the other. The experiments of Schlesinger and Oser[1] would go to prove, firstly, that the arterial anæmia is to be regarded as the stimu-

[1] Wiener med. Jahrbücher. 1872. I.; and *Schlesinger*, Ibid. 1873. I. and 1874. I.

lating cause of the movements of the uterus; and, secondly, that the uterine contractions are caused by excitement from the central organs. In this experiment the exclusion of the flow of arterial blood to the brain, by ligaturing all the blood-vessels leading to the brain, produces in about half a minute general contraction of the uterus. The abortions produced by ergot-poisoning are thus accounted for by its increasing uterine contractions.

The hypothesis that the uterine contractions are produced by alterations in the distribution of the blood might be thought to be supported by the experiments of S. Mayer and Basch, which show that arterial anæmia of the intestine stimulates it to violent peristaltic contraction. This circumstance accounts for the diarrhœa which sometimes sets in even in the later part of the course of poisoning by ergotine and ergot of rye.

The action of ergot on the brain and the spinal marrow is not very marked in the human subject, but may be more accurately ascertained by experiments on animals. Ergotine, injected in sufficient quantities into frogs, paralyzes voluntary movements as well as reflex actions. Zweifel regards the influence of ergot upon the brain and spinal marrow, which it paralyzes, as its main action. The paralysis begins at first in the hind legs and advances continuously forward; the limbs recover their power in the same sequence. With moderate doses the whole frog may be paralyzed, so that only cardiac and respiratory contractions continue. In mammalia also ergotine produces a remarkable unsteadiness of gait and general paralysis which lead to death. The spinal cord is therefore affected by the active principle of ergot; it is stimulated for a short time and then paralyzed, and this paralysis may, when the doses are sufficiently large, extend even to the centres of respiration and cardiac contraction.

It appears very probable, from some symptoms in chronic ergotine-poisoning, that this substance exerts some influence on the sensory nerves, but it has not yet been determined satisfactorily by experiment. The symptoms seem to imply a primary stimulation and subsequent paralysis of the sensory nerves.

A few words must be added as to the influence of ergot upon the fœtus in utero. The influence of this drug upon the child

has been over-estimated. It has been asserted that the number of still-born children is increased by the administration of ergot; further, it has been stated, as the result of observation, that the pulsations of the child are diminished in frequency by the mothers having taken ergot; finally, the contractions of the uterus are said to injure the child by compressing its body.[1] All these observations have been questioned in recent times, and no accoucheur hesitates to make use of this drug if the symptoms indicate its administration. In the same way the effect of ergot in producing abortion has been considerably exaggerated. It very seldom succeeds in expelling the fœtus, if the conditions for its expulsion have not arisen in some other way.

In conclusion, it must be stated that there is perhaps no poison respecting which our knowledge rests on so comparatively weak a basis as this ergot, and that we can only succeed in obtaining really satisfactory information on the subject when it has become possible to prepare the active principle of ergot as a pure substance. Till that time the preparations offered for sale, as well as those prepared by particular investigators (such as Wernich and Zweifel) will differ from one another in their effects.

Results of Autopsies in Acute Ergot-Poisoning.

Reports of autopsies in the case of persons who have died of acute ergotism are extremely rare. In Richter's case, quoted above, respecting a young woman, twenty-three years of age, in a state of pregnancy, in whom the expulsion of the fœtus, six to seven months old, actually did take place, the observations at the autopsy were considerably modified by the violent hemorrhage, probably fatal, which occurred during that act. Injection of the vessels of the mucous membrane of the œsophagus and the stomach and a few corroded spots were found; small portions of ergot which had been taken were found still in the stomach, and were proved to be such, both microscopically and chemically. In dissection of animals poisoned with ergotine we gene-

[1] *Beatty*, De l'influence du seigle ergoté sur le Fœtus dans la matrice. Journ. des Connaiss. méd. Feb. p. 135. 1845.

rally find highly marked venous engorgement, especially in the abdomen, and above all in the urinary bladder, which is generally distended. But, according to Zweifel's reports, the bladder is sometimes found empty and contracted. What has been written about hyperæmia of the brain and its membranes is to be regarded as at least very uncertain.

Diagnosis and Differential Diagnosis.

The diagnosis of acute ergot-poisoning rests chiefly on the history of the case and on the probable discovery of small particles of ergot in the vomited matters and in the fæces. When ergotine has been administered, especially in the form of subcutaneous injection, the diagnosis of ergotine-poisoning presents formidable difficulties. Diminished frequency of cardiac pulsations, contraction of the arteries, reduction of the temperature, etc., might afford some clue. But none of these symptoms are characteristic enough to exclude with certainty the possibility of other poisonings.

Prognosis.

It has been already stated that acute ergot-poisoning very seldom ends fatally. The prognosis will be the more favorable the more normal the action of the heart before the introduction of the poison, the earlier the occurrence of vomiting, or that a suitable system of treatment was commenced.

Treatment.

The first indication in internal poisoning by ergot and its preparations is the elimination of the contents of the stomach by means of emetics; later on purgatives may be administered to remove the poisonous substances which may be lodged in the intestinal canal. As chemical antidotes for counteracting the effect of the poison introduced, tannin, and substances containing tannin, are the most effective. As to the rest, the treatment must be limited to combating the symptoms produced by the

poison. The principal of these is cardiac asthenia, which requires energetic treatment. Alcohol, ether, camphor, preparations of ammonia, wine, coffee, etc., are the best means of arresting threatened cardiac paralysis. Perhaps nitrite of amyl is a remedy which, by dilating the arteries, may check the supposed accumulation of blood in the veins. At present we have but few observations to help us.

Changes which Ergot undergoes in the Organism.—Tests.

So long as the chemical properties of the active constituent of ergot are not accurately known, and so long as it cannot be isolated in a state of purity, we cannot say what are the changes which it undergoes in the animal organism; and it is equally impossible to venture a positive statement of the mode in which it is excreted. That the active principle of ergot passes into the blood and becomes active there is evident from observation of the symptoms which it produces, while the fact that the subcutaneous injection of ergotine rapidly induces its special action may be advanced as experimental confirmation. Should it be necessary, for judicial purposes, to test for poisoning by ergot, the only basis we have to go upon is the discovery of the remains of the powder of ergot in the matters vomited and in the fæces. As far as our knowledge goes such a test has only once been furnished (in a case ending fatally, which Neubert has reported), by heating the organic substances suspected to contain the poison with alcohol, and then evaporating the alcohol; a residuum was obtained very similar to Wiggers's ergotine, and possessing its qualities, viz.: insolubility in alcohol, ether, and acetic acid, solubility in water only when in combination with mucus, an unpleasant odor, and sharp, bitter taste.

Chronic Poisoning by Ergot.

The long-continued use of ergot, especially in the form of flour, and bread made of flour, often led, in former ages, to fearful devastation of whole races of people, inhabiting more or less

extended tracts of country. The first reports which we possess on this subject date from the ninth century; it is not, however, till later years that we meet with good descriptions of this malady, which fix upon it the undoubted character of chronic ergotism. In the year 1630 Thuillier discovered the cause of this affection, which had till then been attributed to all possible and impossible factors, among which mystic views played the chief part.

Diseases produced by the consumption of food containing ergot appeared in the middle ages as very violent epidemics; but they did not cease, even after the cause of the disease was known; from time to time—often after intervals of ten, twenty, thirty years, and longer—epidemics broke out again, which generally lasted only a year, but sometimes continued through several years; thus, for instance, an epidemic was observed in Switzerland which lasted from 1709–1716. Epidemics more or less severe continued to prevail in the last century; several are recorded even in our own century, and though they may not be equal in extent of distribution to former ones, still they warn us of the possibility that what happened as late as thirty years ago, and even more recently, may occur again under favoring conditions. And therefore we may be permitted to say a few words here on the subject of chronic ergot-poisoning. As above mentioned, chronic ergotism appears in two clearly distinct forms; one form is characterized chiefly by the presence of convulsions, with considerable disturbance of sensation; it is therefore called spasmodic ergotism or "Kriebelkrankheit;" the second form is characterized by gangrene of the face and the extremities, and is therefore called gangrenous ergotism.

Spasmodic Ergotism.

Etiology.

In Falck's[1] treatise on poisoning we find accounts of nineteen epidemics of "Kriebelkrankheit," which appeared chiefly in

[1] Handbuch der speciellen Pathologie und Therapie von Virchow. Bd. II. 1. Abthlg. pp. 319, 320.

Germany, between the years 1556 and 1795. All these epidemics began in the autumn of each year, and generally lasted till the next year, often till the following autumn. They always appeared after corn-harvest in bad and rainy seasons, which were distinguished by failure of crops. It was long unknown what was the poisonous constituent of the flour, but it has now for many years been ascertained with absolute certainty that it is the presence of ergot, while other plants, such as the Lolium temulentum, which some regarded as the cause of Kriebelkrankheit, have been shown to have no connection with it. The wheat which gave rise to this affection always contained a large proportion of ergot, at least one-tenth, sometimes even one-eighth of the whole quantity, as Johann Taube[1] and Anton Scrinci have shown. The circumstance that only those were attacked who had partaken of bread or other food prepared from wheat containing ergot, and the fact that they improved when they ate bread containing no ergot, and relapsed when they returned to the ergotized wheat again, proved incontestably that ergot was the sole cause of the disease. The disease attacked the lower orders rather than the higher, as they are the largest bread-consumers; neither age nor sex was spared, but babes at the breast were never attacked.

The following reports show that even in our own time we are not quite free from this malady. Aschoff[2] describes a house epidemic, which in the very damp autumn of 1840 appeared in a family consisting of eight persons; the illness lasted in each case from three to five weeks, and two children, seven and eleven years of age, died of convulsions on the twenty-first day of their illness. Ditzel[3] describes twenty-four cases of morbus cerealis in that same year, all of which ended in recovery. Puchstein[4] reports the cases of five persons who were attacked with "Kriebelkrankheit" in the village of Stregow in the district of Kamin.

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[1] The older reports of this disease, chronologically arranged, are included in Falck's work, above cited.

[2] Zur Lehre von der Kriebelkrankheit. Casper's Wochenschr. Oct. 1844.

[3] Nachtheilige Wirkung des Mutterkorns. Oppenheim. Zeitschr. März. 1844.

[4] Beitrag zur Geschichte der Kriebelkrankheit. Med. Zeitg. des Vereins in Preussen. No. 2. 1853.

The circumstance that the disease was limited to the members of a shepherd's family, while his neighbors remained free, is attributed by Puchstein to the fact that the neighbors had mixed the flour containing ergot with a quantity of potatoes and barley, whereas the shepherd's family had eaten it unmixed. Heusinger [1] gives a report of an epidemic in the village of Möllnau in Upper Hesse, which lasted from the autumn of 1855 till the summer of 1856. The ergot of brome-grass was the main cause of this epidemic. Ungefug [2] also describes an epidemic in a family at Darkemen, in the year 1845, to which one person succumbed. A similar epidemic in the neighborhood of Holzminden is mentioned by Pockels.[3] Lastly, we have a report by Dr. Flinzer [4] of an epidemic at Auerbach, near Stolberg, in Saxony, in the year 1867, in which there were some deaths. In 400 parts of rye there were 40 parts of ergot; therefore ten per cent. The epidemic attacked a farm-house with six inhabitants.

Symptoms and Course of Spasmodic Ergotism.

When flour strongly impregnated with ergot in the form of bread or other farinaceous food has been eaten for several consecutive days in some considerable quantity, the first symptom of ergot-poisoning makes its appearance in the form of a peculiar irritation of the cutaneous nerves, much like the sensation of an ant creeping over the skin; this feeling is called in German "Kriebeln," hence the name of "Kriebelkrankheit" given to the disease in this country. As to the point of time at which this sensation sets in, cases are known in which the first symptoms appeared as early as the fourth day of partaking of the bread or the flour containing ergot (Flinzer). Yet in some cases it may be borne longer without inconvenience. This depends on the quantity of ergot introduced, and on the relative proportion of bread to it, as also on the quality of ergot itself. It is an

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[1] Deutsche Klinik. No. 20. 1856.

[2] Casper's Vierteljahrschrift für gerichtliche Medicin. etc. Bd. IX. Hft. 1. 1856.

[3] Deutsche Klinik. 1. 2. 1857.

[4] Vierteljahrschr. f. gerichtl. Medicin. VIII. 2. p. 360. 1868.

ascertained fact that this substance in growing old loses its activity and poisonous character, and that it is also deprived of some of its activity by the process of grinding the wheat into flour, and baking the flour, etc. Thus there is a case reported in which several persons consumed in five days twenty-two and a half pounds of ergot in bread without suffering in consequence; whereas, if the same quantity had been taken in a fresh condition, death must have been the inevitable result. This formication continues during the whole course of the illness, and is the last symptom which disappears. It affects chiefly the fingers and toes, but may also extend to other organs, *e. g.*, the hands and arms. In some cases the formication increases to actual numbness, and even to complete anæsthesia of the parts affected. Simultaneously with this formication symptoms set in in the stomach and intestinal canal similar to those described under Acute Ergot-Poisoning. Vomiting and diarrhœa alternate with violent colicky pains; curiously enough, as a rule, this is accompanied with intense hunger.

The patients suffer from insatiable hunger, to satisfy which they devour everything eatable that comes in their way. On account of this symptom, the disease has been entitled Raphania, which name arose out of the mistaken supposition that the wild radish (Raphanus raphanistrum) was the cause of the disease; now it is used as a synonym for ravenous hunger. Another symptom usually present is a peculiar sensation of discomfort, anxiety and weariness, giddiness, and general uneasiness; the patient also complains of distressing pressure in the pit of the stomach, and the formication grows into very acute pain. Then we get involuntary twitchings in various groups of muscles, *e. g.*, in the tongue and in the extremities. These twitchings soon pass into continuous contractions, which specially affect the flexors, so that the arm, *e. g.*, remains fixed in a bent position. This muscular cramp will last a variable time, half an hour or even a whole hour, or more; this cramp is also very painful; from this symptom the disease was formerly called in Germany "die ziehende Seuche," "der krumme Jammer," "die Schwerenothkrankheit," etc. The retching and vomiting are persistent, but the action of the bowels is sluggish. When the contractions

pass off, a state of utter exhaustion remains. But soon the painful convulsion returns and makes the patient moan and groan continuously. The contractions now appear simultaneously in various groups of muscles, the epigastrium is tightly distended, the facial muscles are distorted, the legs are flexed. At the same time, the hands frequently assume a beak-like form, the fingers being contracted towards the middle finger, and simultaneously flexed towards the ball of the thumb; the foot assumes a similar form. The pupils are usually contracted, sometimes distorted; the eyes are fixed. The skin is covered with cold perspiration, the urinary excretion is suppressed; but at the same time there is violent dysuria, dependent on spasm of the bladder. The pulse is weak and low. In severe cases the patient loses the power of sight and speech, of hearing and consciousness. Delirium sets in, the face is pale and sallow, the head, like the body, feels cold, and thus, with the continuance of the convulsions, and gradually advancing cardiac paralysis, death may supervene. This may occur as early as the third day after the beginning of the symptoms, especially when the contractions, as sometimes happens, attack the respiratory and spinal muscles, inducing opisthotonus. The loss of sight may be preceded by all possible visual disturbances, colored vision, double vision, etc. In many cases which do not terminate fatally, cataleptic and epileptic attacks occur, either with or without loss of consciousness.

Of the other organs, the skin is especially under the influence of this poison. Besides very abundant perspiration, pustules often break out, or even larger furunculi. The exanthemata sometimes resemble scabious eczema; they appear in the later stage of the malady, as, *e. g.*, in Aschoff's case, fourteen days after the appearance of the first symptoms of poisoning. But other disturbances of nutrition in the peripheral organs are also reported, as, *e. g.*, whitlows on the fingers, occurring as late as the fourth and fifth week, and diseases of the finger-nails, which are encircled by a dark ring. Cardiac contractions are generally slow and feeble, the arteries are constricted and contain little blood. The respiration is very labored during the spasms, but tolerably regular in the free intervals. When death supervenes,

it is usually not till after a fortnight or later; the convulsions may have ceased, yet loss of sight and hearing with violent headache, stupor, and delirium, may set in, attended with diarrhœa; and thus the fatal stage may assume the form of typhus and general collapse. Death is generally ushered in by either convulsions or paralytic symptoms. The whole form of the illness, therefore, is very variable, and its course highly irregular. The illness may last 4–8 weeks, and even longer. If the case takes a favorable turn, the spasms diminish in number and intensity, the disturbances in the functions of the organs of the senses gradually subside, digestion recovers its tone, and complete recovery may set in, though not for several weeks. In many cases, however, recovery is incomplete, various pains and infirmities remain behind, especially, *e. g.*, muscular weakness and tremor, stiffness in the joints, in other cases actual paralysis and epileptic attacks; in some rare cases melancholia and imbecility are results of this disease; permanent disturbances of visual power are also reported.

Analysis of Symptoms—Nature of the "Kriebelkrankheit."

The symptoms which mark the course of spasmodic ergotism all point to a disturbance of the central nervous system under the influence of ergot: the motor as well as the sensory centres in the brain and spinal cord are first excited, and later on paralyzed, by the poison. There can be no question that the convulsions, the disturbances in the organs of the senses, in the sensorium and in the cutaneous nerves, are of central origin. But the question arises whether this effect of the poison is a direct one, or indirectly caused by the changes in the capacity of the vessels. It is known that convulsions may arise from arterial cerebral and spinal anæmia, as well as from excessive hyperæmia, and more readily so from the former. The disturbances in the organs of sight and hearing are easily accounted for by the anæmia, and, indeed, a series of cases have been recently published of acute amaurosis after acute hemorrhage; now the accumulation of blood in the venous network which we have mentioned in acute ergot-poisoning, is closely analogous to acute

hemorrhage. But although we are led to assign a considerable share in the production of the series of symptoms to constriction of the arteries, it is impossible to exclude a direct influence of the poison upon the nervous system. In Zweifel's late work, as we have already mentioned, stress is laid upon the latter mode of action, and the symptoms of "Kriebelkrankheit" are to be traced to an initial excitement and subsequent paralysis of the central nervous system. Therefore, we refer the reader to the analysis of symptoms given under acute ergotism. There is no doubt that some of the symptoms depend upon the drain of fluid, caused by the repeated vomiting and diarrhœa. But the general symptoms are chiefly the result of the direct action of the poison on the mucous membrane of the stomach and intestine. The vomiting in the later stages of the illness may be regarded as central, and the later diarrhœa is traceable to the altered condition of the blood found in the intestine.

Results of Autopsies.

Frequent as deaths from spasmodic ergotism were in former times, very few good reports of the results of autopsies lie before us. The few physicians who have reported such autopsies are unanimous in stating that putrefaction sets in very rapidly. The heart is found bloodless and flaccid, the lungs in a condition of venous hyperæmia; venous injection of cerebral membranes is very marked. Strongly injected patches are often found in the stomach and intestine, sometimes hemorrhagic and even gangrenous erosions are met with. Evidences of venous hyperæmia are found in the abdominal glands, in the liver, and the spleen, which are somewhat swollen and dark colored.

Diagnosis and Differential Diagnosis.

The diagnosis of chronic spasmodic ergot-poisoning is generally not very difficult, especially as it usually partakes of the character of an epidemic, though of limited extent, and the history is easily obtained. The disease, as such, may be confounded with spinal meningitis, or even with cerebro-spinal meningitis.

But the existence of convulsion of the flexors supplies an essential point of distinction. The absence of fever and the condition of the circulation may also assist in the diagnosis. It is distinguished from strychnine-poisoning by the essential difference between the convulsions in the two cases; strychnine convulsions are constantly reflex convulsions, which is not the case in "Kriebelkrankheit."

Prognosis.

The prognosis in chronic ergotism is different at different times, since the quantity of ergot contained in the wheat of different years varies. Practically, the prognosis depends not only upon the quantity of poison introduced, but upon the individual constitution. Weakly persons, old people, and children succumb more easily to ergotism than young and strong individuals. The prognosis depends considerably upon the time at which the poisoning is recognized, as an early recognition enables us to guard against the further introduction of the noxious substance. In other respects the prognosis is favorable if the convulsions come on at long intervals, if they remain confined to the extremities, if the nutrition of the patient is comparatively unimpaired, if the diarrhœa and vomiting are slight, and if the changes in the circulation are inconsiderable; it is unfavorable if all these symptoms are of an aggravated type. Mobility of the pupils, and a moist, warm skin are favorable signs.

Treatment.

The most important thing is to prevent the disease, which is comparatively easy, as its cause is so accurately known. The rare appearance of this disease in recent times is traceable to a more thorough purification of wheat from ergot, and to the importation of corn from other places into districts in which the crop has failed. Another reason is that, in modern times, people are accustomed to much more variety in their food, and are not limited to one kind as formerly; the introduction of potatoes has no doubt effected an improvement in this respect. Still it may

be well to make the danger of ergot a subject of school-instruction, and to spread this knowledge among the general public at harvest-time in damp years. In practice, the first object must be to prevent further introduction of poison, and to replace the tainted bread by healthy food; the second will be to eliminate any poisoned bread still remaining in the gastro-intestinal region by emetics and purgatives. Drastic remedies are, however, to be avoided, as they may promote the continuance of diarrhœa. Remedies containing carbonic acid are advisable for the excessive vomiting, and moderate doses of opium for the diarrhœa. Cardiac contraction demands close attention, and must ultimately be treated with the usual stimulants. The cramps in the extremities are relieved by friction of the skin, and patients also request that their convulsively contracted limbs be extended. Warm baths are also calculated to suppress or shorten the spasms. It is unnecessary to add that particular symptoms may indicate other remedies.

Changes which Ergot undergoes in the Organism.

There is no doubt that the active constituent of ergot is absorbed into the fluids of the body, and flows with the blood through all the organs. It is probable, but by no means proved, that the excretion of the poison takes place partly through the urine, partly through the intestinal canal; it is further probable that the poison is contained also in some of the secretions, *e. g.*, in the saliva, which accounts for the salivation; but this much is certain, that it does not enter into the secretion of the breast—the milk—for all authors are agreed that sucklings are not affected, even when their mothers are suffering from ergotism; also in most cases the secretion of milk is not altogether suppressed. Whether a part of the poison introduced is decomposed within the body is not known. (See the same heading under Acute Ergot-Poisoning.)

Tests of Chronic Ergot-Poisoning.

The properties of the bread adulterated with ergot should be the first subject of investigation. Bread containing ergot has a peculiar odor, a dark violet color, a sweetish but not exactly unpleasant taste ; the flour, which contains large quantities of ergot, has also the same peculiar taste and a darker color. Small particles can be microscopically detected as belonging to ergot. When flour containing ergot is heated with caustic potash, a very characteristic odor, like herrings or old soap, arises ; this odor lasts a long time, even when only one-seventy-second of ergot is mixed with the flour (Wittstein). Other tests recommended are less constant and not characteristic.

We find some cases reported of illnesses resulting from ergot which, besides the symptoms of spasmodic ergotism, show also symptoms of gangrene in peripheral parts, such as the toes, fingers, etc. These cases form the transition from the spasmodic form of ergotism to the gangrenous, and thus prove that these two forms of disease are really dependent on the same cause, and that both may be regarded in a certain degree as different stages of one and the same disease, stages which, however, have attained a certain substantive form, and by no means necessarily pass into one another, or follow as sequelæ to each other. It is not certainly known why in the one case the ergotism assumes the spasmodic, in the other the gangrenous form. But it appears remarkable that the spasmodic form formerly prevailed chiefly in Germany, while the gangrenous form was found principally in France, and there particularly in the Sologne. But this difference does not hold universally, for epidemics of the gangrenous form have appeared also in Germany, Austria, Russia, and Sweden. It is not known, whether this variety depends upon a difference in the activity of the ergot in different seasons, or whether such changes are the result of some peculiar property of the ground in which the corn grows. In

the Sologne it was generally the ergot of maize which produced the poisonous symptoms, whereas in Germany the ergot of rye was almost exclusively mentioned as the cause of the disease. It is, however, very improbable that the difference between these illnesses is dependent on the different parent plants, because, at least therapeutically, the same effects can be produced by the ergot of maize as by that of rye, when the quantities are equal.[1] It is most probable, then, that there is a simple quantitative difference in the absolute and relative quantity of the poison taken into the system.

Gangrenous Ergotism.

Gangrenous ergotism often raged formidably in vast epidemics in former ages. France and Switzerland were the countries most visited by this disease. Thus Falck mentions thirteen epidemics, from the year 1630 till the year 1820, which were almost all confined to the countries above named, only few cases comparatively occurring in Germany. This form of ergot-poisoning has become much more rare in modern times, and when it does occur it attacks only limited districts, generally only a few families. This diminution is traceable to accurate knowledge of the etiology of the disease, to increased freedom of communication, to the prevalence of mixed diet, etc. Still, that our age is not quite free from gangrenous ergotism is proved by the recurrence of different epidemics in the last thirty years. Bonjean[2] describes one which, in 1844, attacked a family of eight persons in Savoy, and was caused by their partaking of flour which contained about twenty per cent. of ergot. Barrier[3] mentions a not very severe outbreak of gangrenous ergotism in the departments of Isère, Loire, Haute Loire, Ardèche, and Rhone; an unfortunate maize harvest was the cause of this epidemic, about thirty

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[1] *Jobert*. Quelques observations sur les propriétées thérapeutiques de l'Ergot de Olé. Gaz. des Hôpit. No. 37. 1855.

[2] Ergotisme gangraineux developpé chez deux enfants mâles par l'usage d'un pain, qui contenait du seigle ergoté. Compt. rend. de l'Acad. T. XIX.

[3] De l'épidemie d'ergotisme gangréneux observée à l'Hôtel de Dieu de Lyon en 1854 et 55. Gaz. méd de Lyon. No. 10. 1855.

cases of which came under the notice of Barrier. Dr. Helm[1] reports a slight epidemic which broke out among the workmen on the railroad at Brünn, in Moravia, during the months of November and December.

Etiology.

The cause of gangrenous ergotism, as we have said, is doubtless to be found in the ergot which is consumed with flour and bread. All that has been said about spasmodic ergotism applies here, so that we need only refer to that section. As has also been said, gangrenous ergotism is most probably only a quantitative aggravation of spasmodic ergotism, *i. e.*, poisoning produced by large quantities of the ergot.

Symptoms and Course of Gangrenous Ergotism.

In the beginning of the illness we find the same symptoms as in spasmodic ergotism; the first symptom being violent cutaneous irritation, formication, and modification of sensibility in the peripheral nerves. Identical symptoms also appear in connection with the stomach and intestinal canal—retching, nausea, vomiting, and diarrhœa; the symptoms connected with the central nervous system are also the same—headache, and giddiness; occasional contractions of the flexor muscles are also observed; the changes in the cardiac contraction and in the fulness of the arteries, the disturbances in the activity of the organs of the senses are identical with those of spasmodic ergotism. This condition may last a longer or a shorter time, so that the epidemics may be distinguished as malignant or mild. The symptoms which characterize gangrenous ergotism as such often appear within from two to seven days, but are frequently delayed for two and three weeks. An erysipelatous redness shows itself on some spots in the periphery, most frequently on the toes and feet, but also on the fingers and hands, more rarely on the ears

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[1] Ueber Ergotismus gangrænosus. Wochenblatt der k. k. Gesellschaft der Aerzte zu Wien. No. 11. 1856.

and the nose; soon after the epidermis is raised like a bladder by serous exudation; the ichorous contents of this are soon discharged, and a gangrenous spot more or less large is left. Then dry gangrene develops very rapidly at the affected spot.

The part affected is very painful while the redness is invading it, but later on it becomes quite insensible. On account of the erysipelatous redness the disease was called Ignis sacer in former ages. The gangrenous spot may exhibit either the dry or moist form, according to whether the discharge was checked or encouraged; upon this also depends the greater or less intenseness of the odor of putrefaction. In some cases the gangrene was limited to one or more toes, sometimes only to single phalanges; in other cases, however, the entire foot or hand was affected; not infrequently the gangrene extended to the trunk; it was possible for the patient to lose both feet or both arms. Indeed, a few cases are reported in which all four extremities were lost. The gangrenous parts become separated from the healthy tissue by a well-defined line of demarcation, and the affected part may either fall off of itself, or must be removed by an operation. This process of demarcation is often attended with serious disturbances of the general condition of the patient; sometimes a modified form of continued fever is developed, followed by phthisical changes; in a few cases, from absorption of ichorous matter, pyæmia and septhæmia set in, and are, of course, fatal. When the gangrene was confined to parts of minor importance, the patients usually recovered; greater losses were naturally more frequently fatal. In some cases obstinate diarrhœa brought on marasmus and death, even when the extent of the gangrene was not very considerable. We must mention, however, that in many cases the diseased process did not advance beyond the erysipelatous redness; marked cyanosis may be observed, and yet a separation may take place, and the circulation be restored. The duration of the entire illness is very variable, and may be protracted through several months. In favorable cases the course is ended in a few weeks.

Analysis of Symptoms—Nature of Gangrenous Ergotism.

For the elucidation of most of the symptoms which have been mentioned, it is sufficient to refer to what has been already said of spasmodic ergotism. The gangrene is the only new symptom in gangrenous ergotism. This form of gangrene, like all other forms, depends on the fact that the part affected is deprived of its blood-supply, and its nutrition thereby arrested; consequently it must pass into a state of decomposition. The only question which can be advanced here is, whether it is inflammation which leads to gangrene, or whether the process is of a non-inflammatory character, resembling that which occurs when all the vessels going to a limb are ligatured. When we consider that the initial so-called erysipelatous redness is simply dependent on the cyanosis, and that these spots are not, as in a case of inflammation, hot and swollen, but, on the contrary, they become very cold, and warmth cannot be restored in them, and that the affected limb is not at all swollen, the hypothesis that such a gangrene is of an inflammatory character must *a priori* be rejected. When we further reflect that there is no fever at the outset, the second hypothesis becomes still more probable. Such simple exclusion of an extremity from its ordinary blood-supply is quite conceivable from our current views of the action of ergot on the vessels and the distribution of blood.

The contraction of the small vessels, especially of the arteries, by ergot, particularly when the vis a tergo, *i. e.*, the cardiac contraction, is in a remarkable degree simultaneously affected by this poison, may lead to a complete emptying of blood not only in the separate smaller vessels, but also in the larger vascular trunks; and it is conceivable that by the failure of the blood-supply the arteries themselves (*e. g.*, in the intima) may become diseased, so that thrombi readily form in them, and so the whole process may be characterized as thrombotic.

This thrombotic process is likely to occur in those cases of slow progress in which gangrene does not set in till very late. The throwing off of the gangrenous limbs, the suppurative fever, the pyæmia and hectic are in accordance with general pathologi-

cal knowledge. If we ascribe the lion's share in the total effect of the poison to the action of ergot on the nervous centres, and regard the contraction of the vessels as a secondary influence, as Zweifel does, the gangrene is certainly not very easy of explanation. Zweifel lays stress on the fact that gangrene from bed-sores arises very readily in parts which from any cause have lost their sensibility, and he is disposed to regard the gangrene in chronic ergotism as a kind of decubital gangrene, especially when it attacks chiefly the lower extremities, as these have to support, for the most part, the pressure of the whole body. This view, which has much to recommend it, does not, however, explain those cases in which gangrene attacked the upper extremities, the nose, and the ears.

Results of Autopsies.

Very few autopsies have been performed on persons who have died of gangrenous ergotism, although material was not wanting, at least in former centuries. The reports that we possess contain nothing that is characteristic of this poison; that the gangrenous parts have been found in different stages of mortification, and that inflammatory action existed around them, was to be expected. The most striking fact is that mentioned by Bonjean, who states that he found the arteries leading to the gangrenous limbs in a healthy condition; Barrier, on the contrary, maintains that he found a primary disease of the arteries; he, however, stands alone in this statement.

Diagnosis and Differential Diagnosis.

The recognition of this disease is not difficult, if the mode of development of the gangrene is observed, and if the history and the etiological conditions are taken into consideration. The hypothesis of inflammatory gangrene will thus be excluded *a priori*. The only disease for which it might be mistaken is senile gangrene, for this may arise, especially if the arteries are affected, without inflammatory and feverish symptoms. The

condition of the heart, the full or empty state of the arteries and veins, and the circumstance that gangrenous ergotism attacks individuals of all ages, and generally several simultaneously, will enable us to distinguish between them. The season of the year will also greatly assist in the diagnosis.

Prognosis.

The prognosis rests chiefly upon the quantity of poison taken, and upon its activity, which, as has been stated above, differs according to the time and manner of consumption, the preparation of the bread, etc. When gangrene has once broken out, the prognosis will mainly depend upon its extent. The condition of the patient as to nourishment, the possibility of keeping up his strength, the state of cardiac action, will naturally have an important bearing on the prognosis.

It may be stated in general that gangrenous ergotism is a very dangerous disease ; there have been epidemics in which sixty per cent. and more died. Of the epidemics which have occurred in modern times the mortality never exceeded ten per cent. It is needless to say that the patients, when they escape with life, have lost one or other limb.

Treatment.

In the outset of the case emetics and purgatives must be administered, to eliminate any poison remaining in the intestinal canal ; the second measure of importance will be to avoid the use of ergot by introducing a suitable diet ; no bread ought, therefore, to be allowed, but milk, meat, etc. In the further management of the case it will be advisable to increase the blood-pressure by stimulants, so as, if possible, to avert arterial anæmia in the peripheral parts, before gangrene appears. When the erysipelatous redness is seen on any spot, the supply of blood should be promoted by hot fomentations and warm bathing locally, in order, if possible, to ward off venous hyperæmia and stasis. After gangrene has set in, a strengthening *régime* may

prevent its spreading, and at the same time hasten the throwing off of the gangrenous parts. As dry gangrene is generally to be preferred to moist, it may be advisable to remove the epidermis from the gangrenous parts; this leads to drying up, and at any rate diminishes the formation and absorption of ichor. The removal of the mortified parts after the formation of a line of demarcation is the business of the surgeon. The anæsthesia, neuralgia, paralytic symptoms, etc., which sometimes remain behind, are to be treated as substantive diseases.

The use of tannin—recommended by Griepenkerl as a chemical antidote—can, naturally, be of use only so long as the poisonous bread, etc., remains in the stomach. Certainly no combination between tannin and ergotine can take place in the blood. Nobody, in these days, will venture to suggest the venesection which was so freely adopted formerly.

The use of narcotics deserves the greatest attention in all stages of the disease. The nature of the symptoms must guide our decision whether opium, morphine, chloral, or other narcotics should be administered in the special case.

For the testing of the poison in bread, flour, etc., and the changes which ergot undergoes in the organism, we refer the reader to what has been said in the previous section.

Poisoning by Poisonous Fungi.

The study of poisonous fungi is one of the most difficult in toxicology; and it is so because not only is our acquaintance with the different varieties and species of these fungi very limited, but also because we know little or nothing about the active poisonous principles contained in them. Some authors pronounce almost all fungi to be poisonous, whilst others say that very few are so.

This difference of opinion arises from the fact that some consider certain fungi to be poisonous because they may have produced symptoms of poisoning in those who have partaken of them, and they do not consider whether it is that these fungi

contain an integral poisonous constituent, or whether other circumstances have tended to make the eating of them injurious. If we assert that a fungus is poisonous, we must be able to prove that it, taken as a plant, contains a substance which, under ordinary circumstances, acts poisonously on the life and functions of the human or animal organism. If a fungus does not produce poisonous effects under ordinary circumstances, but leads to symptoms of illness when special conditions prevail, the fungus, as such, is not to be designated as poisonous. Now there certainly are fungi enough which may be eaten with perfect safety in an ordinary way, but which occasionally cause fatal illnesses.

It is, therefore, important, in the first place, to become more intimately acquainted with these special circumstances. Many persons are attacked with sickness more or less violent from eating perfectly unsuspected mushrooms, while others can eat an equal quantity of these same mushrooms, prepared in the same way, and not suffer in the least. This difference is traceable to individual peculiarities, to a sort of idiosyncrasy.

A further fact is that mushrooms are very apt to create indigestions and gastric and intestinal catarrh, so that the consumption of large quantities of absolutely harmless mushrooms may lead to these complaints with some severe symptoms, which may be taken for symptoms of poisoning.

Again, mushrooms are very watery substances; they contain up to 90 per cent. of water, but they are also comparatively rich in vegetable albumen, so that they contain between 3.2 and 7.2 per cent. of nitrogen (Schlossberger and Doepping). Substances so composed become very easily decomposed, and the products of this decomposition may, as in the case of meat, cheese, sausages, and other kinds of food, act very injuriously on the organism, especially the alimentary canal, and may, under certain circumstances, even produce fatal effects. But these occurrences do not furnish us with data for concluding that the mushrooms are in themselves poisonous.

It would appear, from many cases on record, that the process of decomposition may be furthered by the place in which mushrooms are found, their age, the conditions of weather, by their

being left a long time after gathering, and many similar circumstances, so that mushrooms, in themselves, may come to act injuriously. It must be left an open question whether the method of cooking mushrooms has any influence in this direction, or whether they can, by culinary art, be made more or less digestible in the stomach.

A few examples may be quoted from reports of cases in elucidation of our theory.

The Morchella (morel) and Helvella esculenta are rightly regarded as eatable fungi and much esteemed by gourmands, and yet they have very often produced symptoms of poisoning. Thus Dr. Keber[1] relates the history of the poisoning of six persons, who, after partaking of these fungi, were attacked with vomiting and diarrhœa which lasted for sixty hours. As sequela of the acute gastro-intestinal affection, they all showed symptoms of icterus catarrhalis. In their case it was expressly stated that the morels had been gathered in very damp weather and not thoroughly cleansed. Dr. Schubert[2] reports the poisoning of two children of eight and four years of age respectively, after eating morels. The children were taken ill about six hours after with vomiting and pain in the bowels, and died in convulsions and sopor twenty-one and forty-five hours respectively after the introduction of the fungi, while none of the other members of the family suffered—a proof that children succumb more readily to the action of fungi than adults.

The Morchella and Helvella contain a good deal of albumen and fat. O. Kohlrausch[3] found in the dried Morchella esculenta 35 per cent. of protein and 2.39 per cent. of fat; in Morchella conica 2.96 per cent. of protein and 2.4 per cent. of fat; in Helvella esculenta 26.6 per cent. of protein and 2.2 per cent. of fat. On the other hand, common mushrooms contain only 17.0 of albumen and 1.4 per cent. of fat. Accordingly poisonings by mushrooms

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[1] Vergiftungszufälle nach dem Genusse der Helvella esculenta. Preussische Vereinszeitung. No. 32. 1846.

[2] Aeussern die Morcheln zuweilen giftige Eigenschaften? Casper's Wochenschrift. Dec. 1844.

[3] Ueber die Zusammensetzung einiger essbaren Pilze mit besonderer Berücksichtigung ihres Nahrungswerthes. Göttingen. 1867. Dissertation.

(Agaricus campestris) are much more rare, although they do occur after decayed mushrooms have been eaten.

Slighter poisonings, characterized by vomiting, diarrhœa, and slight collapse are reported as the result of almost all edible fungi.

The warming-up a second time of dishes containing mushrooms very frequently leads to illnesses, as is proved by many cases on record.

As regards fungi which are constantly poisonous under ordinary conditions, and which must therefore be regarded as actually poisonous fungi, we may with confidence accept the classification of Th. Husemann,[1] who specifies as actually poisonous fungi only Amanita muscaria, Amanita phalloides, Russula integra, Boletus luridus, and their varieties. To these belong Agaricus integer, fœtens, bulbosus, rimosus, fastibilis, crustuliniformis, and a few others. These fungi are poisonous: *i. e.*, they contain as integral constituent a substance which acts destructively upon animal life—a poisonous substance.

Disease through Decayed Fungi.

Symptoms and Course.

It is characteristic of all diseases caused by the fungi usually eaten that they produce violent gastro-intestinal symptoms. As a rule, the symptoms appear after six or eight hours, seldom earlier, frequently later, so that, in some cases, the first symptoms of illness do not set in till after eighteen to twenty-four hours. They usually begin with pains in the stomach and intestine; violent colic is the earliest symptom, soon followed by great nausea, with increase of salivary secretion, and then vomiting. This vomiting is seldom over at once; it is generally repeated at longer or shorter intervals, and may last three days and even longer. Soon after the vomiting begins diarrhœa sets

[1] Ueber die medicinische Bedeutung der Pilze mit vorzugsweiser Berücksichtigung ihrer toxischen und diätetischen Eigenschaften. Schuchardt's Zeitschrift f. pract. Medicin. 1865. III. Heft. p. 221 ff; and *Husemann's* Toxikologie. 1862. p. 381.

in, and it may also last a long time. At first the vomited matters as well as the fæces contain the remains of the fungi consumed. These are only recognizable for a short time in the vomited matters, as the stomach soon gets wholly rid of its contents. But the rudera of the fungi are generally found in the fæces even on the second and third day; therefore they remain a comparatively long time in the intestinal canal. But even when the last traces of the mushrooms have been eliminated by the evacuations, this simple removal of the noxious substance by no means puts an end to the vomiting and purging, but purely serous evacuations, more or less profuse, follow, very like the rice-water stools which are characteristic of European and Asiatic cholera. The gastro-intestinal symptoms are directly followed by those of acute drain of fluid. The plumpness of the skin disappears, the eyes sink back in their orbits, the features become pinched and cold, slight cyanosis spreads over the whole body, cardiac contraction becomes insufficient, respiration is labored, and convulsions appear in different groups of muscles, while the patient suffers from insatiable thirst. In some cases these symptoms are succeeded by a condition of sopor, and sometimes, with children, by general convulsions. These latter symptoms have given rise to the belief that an actual poison is developed in decayed mushrooms, which acts toxically on the cerebro-spinal nervous system. We incline, however, to the view that the acute drain of fluid and the disturbance of circulation inseparable from it, together with the imperfect decarbonization of the blood, produce this state of sopor, and may also cause the convulsions, especially in children, whose reflex inhibitory apparatus is decidedly less energetic in its action than that of adults, so that it is quite unnecessary to assume the existence of a poisonous substance which has not been detected.

It is self-evident that this choleraic condition may kill children and weak and elderly people. In such fatal cases collapse advances gradually, carbonic acid poisoning gains ground more and more, and so the scene may close in an algid stage, even after the illness has lasted five or six days. As a rule, however, these cases end in recovery, either because the acute drain of fluid does not reach so alarming a height, or because the physical

constitution overcomes that and its consequences. Convalescence is generally tolerably rapid, and recovery complete. Only in some rare cases it is a long time before recovery sets in.

Results of Autopsies.

Such reports of autopsies as we possess yield no characteristic results. The signs of acute gastric and intestinal catarrh, and the evidences of inspissation of the blood and of death brought on by cardiac paralysis are the only more or less constant phenomena. In some cases, especially when death supervenes soon, remains of the fungi may be found in the intestinal canal, which may determine the diagnosis.

Diagnosis and Differential Diagnosis.

The recognition of the illness described as arising from mushrooms depends chiefly on the history and then on the inspection of the evacuations. If these criteria fail, it is often impossible to differentiate from other diseases—cholera, acute gastric and intestinal catarrh—and only a chemical examination can prevent its being mistaken for arsenic-poisoning. The question whether it is caused by poisonous fungi can only be answered by examination of the mushrooms which have been eaten. As to the rest, the more purely the disturbances are gastro-intestinal, and the fewer the other symptoms, the safer the diagnosis that only simple, and not poisonous, mushrooms are the cause of the illness.

Treatment.

The treatment of this illness brought on by decayed mushrooms consists naturally in procuring the discharge from the stomach and intestines of the injurious substances which have been introduced, as quickly and completely as possible. All kinds of emetics and purgatives may be used for this purpose; yet oleaginous aperients are preferable to saline in case any really poisonous fungi should perchance have been eaten. The

attention of the physician will naturally be directed to the consequences of acute drain of fluid, disturbances in circulation and respiration. He will try to avert collapse by administering stimulants in all possible forms—alcohol, ether, camphor, etc.; he will strive to overcome the subjective and objective dyspnœa by stimulating the skin, to resist the tendency to over-chilling of the body by the application of heat, to relieve the intolerable thirst by internal administration of ice, and by the use of opiates to moderate the subjective sufferings of the patient, and to diminish the hypercatharsis.

With regard to poisoning by actually toxic fungi, intoxication with the fly-fungus (Amanita muscaria) is of most interest to us.

Poisoning with Amanita Muscaria.

Fly-Fungus—Muscarine.

It is not only the frequent recurrence of this kind of poisoning which claims the attention of the practical physician, but the fact that we have learned to recognize the poisonous principle of the fly-fungus in muscarine, and we can follow experimentally its mode of action.

Various investigators in former times had endeavored with imperfect success to isolate the poisonous agent in the fly-fungus and prepare it in a purer condition, but O. Schmiedeberg and R. Koppe[1] were the first to procure from Amanita muscaria an alkaloid which possesses distinctly poisonous properties and fully accounts for the action of fly-fungus-poisoning. O. Schmiedeberg and his pupils have so thoroughly studied this alkaloid, as well in its chemical as in its physiological properties, that muscarine may be counted among our best-known poisons.

Muscarine is a colorless syrupy mass without odor or taste,

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[1] Das Muscarin, das giftige Alkaloid des Fliegenpilzes, seine Darstellung, chemischen Eigenschaften, physiologischen Wirkungen, toxikologische Bedeutung und sein Verhältniss zur Pilzvergiftung im Allgemeinen. Leipzig. 1869. F. C. W. Vogel.

readily soluble in water and absolute alcohol, insoluble in ether and chloroform ; it forms salts with acids, as, *e. g.*, with sulphuric acid a crystalline salt, which deliquesces when exposed to the air. In a free condition muscarine has a very strong alkaline reaction. The quantity of this alkaloid present in the fly-fungus is not exactly determined ; the preparation of it is very complicated, and the portion extracted forms about one-fifth per cent. of the dry fungus.

Etiology.

As poisoning by pure muscarine has never yet taken place in the human subject, but the fly-fungus is always the agent by which it is induced, a few words must be said about this fungus. An infusion or simple watery extract, as well as the juice or small particles of the fresh fungus, acts poisonously on flies, but when dried it loses this property. In addition to muscarine, which is innocuous to flies, this fungus contains another substance, which is poisonous, at least to flies, and which is either destroyed or disappears when the fungus is dried.[1] Another body is also found in this fungus, as Schmiedeberg and also Harnack[2] have shown, a body chemically related to muscarine, amanitine, which exercises no influence on animals. This amanitine (Harnack) most probably passes directly into muscarine when combined with oxygen. In comparing the chemical composition of these two bodies, we find simply one equivalent more of Θ in muscarine than in amanitine. The double chloride of gold and muscarine is, according to Harnack, $= \Theta_5H_{14}N\Theta_2Cl + AuCl_3$; the same salt of amanitine $= \Theta_5H_{14}N\Theta Cl + AuCl_3$. Harnack considers it probable that amanitine is identical with chlorine. The fly-fungus acts poisonously upon human beings in proportion to the amount of muscarine it contains.

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[1] Perhaps the substance which is poisonous to flies is that fugitive body which Borntraeger and Kussmaul obtained by distilling the fly-fungus, and which was like a fatty acid, and when one drop was given to a rabbit killed it, although rabbits steadily resist the action of muscarine. Verhand. d. natur. med. Vereins zu Heidelberg. I. p. 18. 1857.

[2] Untersuchungen über Fliegenpilz-Alkaloide. Arch. für experimentelle Pathologie und Pharmacologie. IV. Bd 3. Hft. p. 168 ff. 1875.

The common cause of muscarine-poisoning is eating the fly-fungus, either from its being mistaken for edible fungi, especially for Amanita cæsarea (the so-called golden agaric), or from ignorance of its poisonous qualities. The fly-fungus appears in our woods between August and October; its cap (pileus) is red, reddish yellow, or yellowish, and bears white scaly warts; its edge is furrowed with white; the flesh is white, and under the outer skin is surrounded by a reddish-yellow rim; the stem is knotty or hollow with a loose white ring; below it is smooth, and close to the ground knobby with an excrescent scaly rind. The lamellæ are white or yellow (Husemann).

Poisoning by means of this fungus was more common formerly than now, an advance which depends on the general spread of the knowledge of its poisonous properties; yet there are very recent reports of this kind of poisoning. Thus, Wutscher[1] reports the poisoning of a man of sixty, and a woman forty years of age; the latter, half an hour after partaking of cooked fly-fungus was attacked with symptoms of gastro-enteritis, twitchings, extensor cramps, and disturbances of vision; in the case of the man, the symptoms were less rapidly developed, and consisted chiefly of excitement and disturbance of the sensorium. Both recovered. Two cases reported by Cosserat,[2] also terminated in recovery. In the year 1859 five French officers at Corte, in Corsica, died from eating a dish of this fungus.

Pathology.

Symptoms and Course.

The symptoms of poisoning appear very soon after the fungi have been eaten; usually not later than half an hour to an hour. But sometimes a longer period of twelve hours and even more elapses before actual symptoms of poisoning appear. These differences as to time depend less on individual peculiarities than on the greater or less quantity of the fungi consumed, and the

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[1] Wiener med. Presse. 17. 1872.

[2] Union méd. 131. p. 714. 1873.

rapidity or otherwise of absorption, which, as is well known, may be promoted or hindered by a number of factors. Violent gastric symptoms are scarcely ever quite absent in a case of poisoning with Amanita muscaria, although the colicky pains, and especially the vomiting and diarrhœa, seldom reach such a height as in cases of the introduction of decayed edible mushrooms. There are even numerous cases on record, in which the gastric and intestinal symptoms have been only secondary, while disturbances of the central nervous system formed the more prominent main features.

The action of this poison generally sets in with more or less violent colic, accompanied with vomiting and subsequent diarrhœa. The excreta contain remains of the fungi which have been eaten. To these symptoms are added cerebral disturbances; the patients think they are drunk, become violently excited; thus, *e. g.*, a girl who had eaten some of these fungi ran about the house in her shift, knocked her head against the wall, and screamed like a person possessed (Cosserat); others suffer from disturbed vision; they see everything dimly, as if wrapt in a mist; things float before their eyes; attacks oi an epileptic nature and actual trismus have been observed. Then a state of sopor gradually sets in, in which the excitability of the sensory and reflex nerves is more or less lowered or quite destroyed. The pulse is, as a rule, retarded, the arteries are constricted, the pulse becomes thread-like, the respiration is generally short and stertorous, the pupils are dilated, the extremities and the features are cold, and death may supervene from progressive loss of cardiac power. If the case takes a favorable turn the patient awakes again out of the state of sopor, his pulse becomes quicker and stronger, his respiration freer, and in a longer or shorter time complete recovery sets in. The more rapid the awakening out of sopor, the more rapid the restoration to health. In slighter cases and with judicious treatment sopor may be recovered from, even after it has lasted from six to eight hours. The period of duration of the whole course of muscarine-poisoning is very different; it is especially dependent on the quantity of poison introduced, on absorption, the occurrence of vomiting, etc.

Death may supervene in a few hours (six to twelve) after the

eating of the poisonous fungi, but usually the course is more protracted, so that the fatal result occurs towards the end of the second or third day. The cases which terminate in recovery are almost always of longer duration. It is impossible to state precisely the quantity of fly-fungus which is sufficient to produce poisoning, but it is certain that even small portions may give rise to violent symptoms. Of pure muscarine, according to Schmiedeberg and Koppe, from an eighth to a fifth of a grain (eight to twelve milligrammes) are sufficient to destroy life in a cat in eighteen to fifteen minutes, and from one-twenty-second to one-sixteenth of a grain (three to four milligrammes) to kill it in two to twelve hours. One-thirteenth of a grain (five milligrammes) of muscarine produces in the human subject myosis, loss of focalizing power, abundant secretion of saliva, determination of blood to the head, flushed face, perspiration over the whole body, giddiness, anxiety, griping and rumbling in the bowels, and weight in the head (Schmiedeberg).

Analysis of Symptoms—Nature of Muscarine-Poisoning.

The symptoms produced by muscarine in animals entirely correspond to those which poisonous fungi produce in the human subject. In cats we observe increased salivary secretion, vomiting, diarrhœa, rumbling in the bowels, wabbling, staggering gait, contraction of the pupils, frequency of respiration, dyspnœa. The vomiting and diarrhœa subside, respiration becomes less frequent, convulsions set in, respiration ceases, death supervenes. It appears, then, that the gastro-enteritic symptoms also are dependent on muscarine alone, and not on other substances mixed with it. The intestine, under the influence of muscarine, becomes subject to tetanic contractions, to which the diarrhœa, constipation, abdominal pains, etc., are traceable.

We are unable to account for this effect on the intestinal muscles, or for the symptoms produced upon the brain.

It is the influence of muscarine upon the brain which induces the inhabitants of Eastern Asia, *e. g.*, the Samoiedes, Ostiaks,

Koraks,[1] and Kamtschadales, to buy these fungi, even at a high price, and consume them. They become at first very cheerful and merry, and subsequently fall into a kind of sopor, from which they awake in a state of exhaustion. The passion of these races for this species of intoxication is so great that the poorer people drink the urine of the rich who have eaten these fungi in order to procure this intoxication. This custom leads us to conclude that muscarine passes unchanged through the blood and the organism, and is excreted unchanged in the urine. It appears, from what has been said, that muscarine must first throw the brain into a state of increased excitability and afterwards into a condition of reduced excitability ; it is even highly probable that muscarine first excites and subsequently paralyzes the brain-cells. In this respect muscarine is closely allied to opium, hashish, alcohol, etc.

The influence of muscarine on the heart and its contractions is very remarkable. The motor ganglia in the heart are at first excited, so that at the onset of the case in the human subject we often find increased frequency of pulse. The principal action of muscarine, however, is exercised upon the inhibitory organs. When we inject $\frac{1}{130}$ of a grain (half a milligramme) subcutaneously into a frog, or bring a solution of muscarine into direct contact with the heart, the heart is almost immediately arrested in diastole. But if, during this suspension of cardiac action induced by muscarine, we irritate the heart in any way, it contracts—a proof that the cause of the cessation does not lie in the cardiac muscle. Section of the vagi has no effect upon this inaction of the heart caused by muscarine ; therefore those inhibitory organs residing in the heart itself are placed in a condition of great excitement by muscarine, and this excitement is powerful enough to paralyze all the contractile power of the heart. It is these same inhibitory organs which are paralyzed by atropine.

This influence of muscarine upon the inhibitory organs in the heart must produce an initial retardation of the heart-stroke,

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[1] *Kenan*, Auszug im Jahresberichte über Pharmacognosie, etc. von Wiggers u. Husemann. 1872. pp. 534–535.

succeeded by absolute cessation, especially when large quantities of muscarine have been conveyed into the blood.

In the early stage of the action of muscarine respiration is more frequent and labored than in the natural condition; later on there is a steady diminution of the frequency of respiratory movements, till at last they cease altogether. These symptoms in the respiratory apparatus proceed from an initial excitement and subsequent paralysis of the central organ in the medulla oblongata which governs respiration.

The blood-vessels are constricted for a short time in the outset of muscarine action, and afterwards dilated, as Bogosslowsky[1] has observed. This vascular dilatation, combined with the diminution of frequency of cardiac pulsations, causes a decrease of blood-pressure, amounting sometimes to one-third of the total amount.

The flow of saliva which attends muscarine-poisoning is the consequence of an exciting influence exercised by muscarine upon the peripheral extremities of the secretory nerves; at least we are led to this conclusion by the circumstance that section of these secretory nerves does not affect the secretion of saliva. Prévost[2] states that he has directly observed in the dog an increase in the secretion of the pancreatic juice under the influence of muscarine. He also asserts that the secretion of urine and bile is promoted by muscarine. It would appear that these effects are only dependent on the change in the circulation, and it is certainly probable that these effects are only observable in the first stage of muscarine action, before blood-pressure has been reduced; once it is reduced, an increase of the secretion of urine is scarcely conceivable.

We must now return to the changes in power of vision. Krenchel[3] has published a very good report of the changes of this kind produced by muscarine. Even small doses of muscarine lead to disturbances in the accommodating power, which are

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[1] Centralblatt für die med. Wissenschaften. 97. 1870.

[2] Gaz. méd. de Paris. 4. Sér. T. 3. p. 243; and Compt. rend. T. 49. p. 381.

[3] Ueber die Wirkung des Muscarins auf Accommodation und Pupille. Arch. für Ophthalmologie. Bd. 20. Abthl. 1. p. 135 ff.

characterized as accommodation-convulsions. With somewhat larger doses a not very marked contraction of the pupils, myosis, sets in. This myosis depends on excitement of the sphincter iridis itself, or on that of the oculo-motor nerve which governs it. The hypothesis of paralysis of the dilatator pupillæ or of the sympathetic nerve connected with it is inadmissible. Most of the experimental facts quoted in this section are taken from the work of Schmiedeberg and Koppe, already mentioned; the report of Bogosslowsky also, who experimented with a very powerful extract of fly-fungus, coincides with theirs in most points.

Results of Autopsies.

The results of autopsies performed upon persons who have died of poisoning from fungi are by no means characteristic. The signs of acute catarrh are more or less pronounced in the stomach and the intestinal canal; and in most cases remains of the fungus are to be found in the contents of the intestine. As for the rest, the evidences of death caused by cessation of cardiac action or by asphyxia are found. Maschka,[1] who has performed a considerable number of autopsies of this kind, stated that in cases of poisoning by mushrooms especially, the absence of cadaveric rigidity is characteristic. This, however, is an error, for we learn from the experiments of Borntraeger and Kussmaul[2] that cadaveric rigidity was developed very rapidly and with tolerable completeness, but that (and this is very noteworthy) it also disappears rapidly; in the case of rabbits, after four hours. It would appear, however, from the experiments of Maschka and Husemann[3] that fatty degeneration of various organs takes place under the in-

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[1] Einiges über die Vergiftung mit Schwämmen. Prager Vierteljahrschrift. No. 29. 16. July. 1856.

[2] Verhandlungen des naturhistorisch-medicinischen Vereins. zu Heidelberg. I. p. 18. 1857.

[3] Die Pilze in öconomischer, technischer und toxicologischer Hinsicht. A work crowned by the Imperial Academy with the Orfila prize, by E. Boudier. Translated and annotated by Th. Husemann, with two lithographic tables. 1867. p. 181. The title of E. Boudier's work is: Des champignons au point de vue de leurs caractères usuels, chimiques, et toxicologiques. Paris. 1868.

fluence of poisonous fungi in general, and of the fly-fungus in particular. For Maschka found, in dissecting several persons who had died in September, 1854, at Prague and in its suburbs from mushroom-poisoning (apparently Amanita phalloides seu venenosa), numerous ecchymoses on the pleura pulmonalis and costalis, varying from the size of a millet-seed to that of a thaler. He found similar ecchymoses in the liver, in the lungs, in the cardiac muscle, in the walls of the stomach, in the spleen, and in the kidneys. Husemann insists specially upon fatty degeneration of the liver in mushroom-poisoning. Maschka also found the urinary bladder distended with urine; sometimes it was found to reach to the navel. The blood is generally fluid and cherry-colored; it is chiefly found collected in the larger veins.

Diagnosis and Differential Diagnosis.

The recognition of muscarine-poisoning, as such, depends chiefly on the inspection of the matters vomited and the fæces. As a rule, remains of fungi will be found in these. But should vomiting and diarrhœa be absent, as is quite possible, the history of the case will provide important data. The season of the year will also aid the diagnosis, for by far the greater number of cases of fly-fungus-poisoning occur in the mushroom season, *i. e.*, in August, September, and October. As to the rest, one of the prominent symptoms of fly-fungus-poisoning is the marked retardation of respiration and of the pulse; but as these symptoms attend the action of many other poisons, they cannot be regarded as characteristic. It will be quite possible to confound this poisoning with that caused by other poisonous fungi, and this can only be prevented by finding characteristic botanic signs in the portions of fungi found in the vomited matters. It is also possible to mistake the action of this poison for that of narcotics. But alcohol would be readily detected by its odor, opium and morphine by the contraction of the pupils ad maximum (in muscarine-poisoning the contraction is less marked), atropine and hyoscyamine by the great dilation of the pupils. In most cases it will also be easy to exclude the possibility of cerebral disease, and, at any rate, even should paralytic symptoms, contractions,

etc., be absent, the course of the illness and the examination of the fæces will facilitate diagnosis.

Prognosis.

Cases of poisoning by means of the fly-fungus are the most severe of all, and therefore the prognosis is always very dubious. Still a number of factors powerfully influence the final result. In the first place, the quantity of the fungus which has been taken is of great importance, for although small portions of this poisonous fungus have produced fatal consequences, still it is self-evident that the greater the quantity which has been introduced, the greater the danger. The period at which vomiting and diarrhœa (if present) occur is very important for the prognosis; for the same reason, the speedy interference of medical treatment has great influence on the course and the result of the poisoning process. Practically, the greatest stress must be laid upon the state of cardiac contraction and of respiration. In general, final recovery is probable, if death has not supervened on the third day. If this danger be surmounted, we may look for a complete recovery, for, though the period of convalescence may be protracted for weeks, no permanent ill effect of the poisoning remains behind.

Treatment.

When the physician finds that poisoning by fly-fungus is in question, he will naturally seek to further the elimination of the fungi from the system as rapidly as possible, and for this purpose emetics are of the first importance. Still, it must be remembered that in many cases their action is slow, if, indeed, they do not remain absolutely inert. Therefore, very energetic emetics must be employed: tartarized antimony with ipecacuanha in sufficient doses, or vomiting must be induced by tickling the throat and uvula. It is needless to say that the stomach-pump will be ineffectual in this form of poisoning. As we know by experience that these fungi may remain for several days in the intestinal canal, we must endeavor to eliminate them by purgatives. Castor

oil, with perhaps the addition of a drop of croton oil, will prove most effectual; oleaginous aperients are preferable to saline or watery ones, or to those charged with vegetable acids, because muscarine is very readily soluble in water, especially in acidulated water.

Tannin may just be mentioned as at least partially a chemical antidote; but we must not calculate too decidedly upon its success, as it does not throw down muscarine completely.

Schmiedeberg pronounces atropine to be an antidote in the real sense of the word, and states that in many respects and in many of its effects it has a directly opposite influence to that of muscarine on particular organs, even though it cannot be proved that an actually double-sided antagonism exists between the two poisons. In order to place this question in the right light, it is necessary to confront the individual symptoms and effects of the two poisons with each other.

Muscarine contracts the pupils, atropine dilates them. A pupil contracted by muscarine becomes dilated by atropine, but an atropinized eye is not contracted by muscarine. Muscarine promotes salivary secretion, which atropine has the power of checking; whereas large doses of muscarine fail to remove the dryness which atropine creates in the palate and throat. Muscarine, in the early stage of its action, produces dyspnœa by stimulating the respiratory centre; this disappears under the influence of atropine. Again, the intestinal tetanus which muscarine produces gives way upon the administration of atropine, or it fails to appear in animals which have been previously atropinized. With regard to the heart, the antagonism between the two poisons is very striking. Very small, even minimum doses of muscarine arrest the frog's heart in diastole; a very minute quantity of atropine restores the contraction; and when the animal is first atropinized and then treated with muscarine, the contraction is not arrested at all. It appears, from the investigations of Schmiedeberg and Koppe, and from those of R. Boehm, that both poisons act, though in opposite senses, on the inhibitory apparatus in the heart, but that the paralyzing action of atropine is more powerful than the stimulating effect of muscarine. We conclude, then, that atropine may be very effectual as an anti-

dote to muscarine-poisoning, whereas muscarine exercises no important influence against atropine-poisoning.

It is proved by some experiments of Schmiedeberg and Koppe, that animals are but slightly affected by even fatal doses of muscarine, when they have been previously injected subcutaneously with small quantities of atropine.

In clinical treatment, therefore, we would earnestly recommend the administration of small doses of atropine ; larger doses must be avoided, lest they should produce atropine-poisoning. No experiments on the human subject have been as yet reported.

For the rest, the treatment must be guided by the symptoms, and especially by the condition of the respiration and circulation. Cutaneous irritation and internal stimulants may be indicated.

Changes which Muscarine undergoes in the Bodies of Animals.—Tests for Muscarine.

Muscarine is very readily soluble in water; indeed, we have only to cut up the fungi, lay them in water acidulated with acetic acid, and press out the juice; this process frequently repeated will render the fungi completely innocuous, so that they may be eaten without danger. The liquid in which they have been expressed becomes of course poisonous through this process.[1] This ready solubility of the poison sufficiently accounts for its rapid absorption ; that the poison is not readily altered is proved by the circumstance that it is not decomposed by the boiling and drying of the fungi, and that it passes out of the system unchanged in the urine, as is proved by the report given above of the intoxicating effect of the urine of those who consume these fungi.

Should it be necessary to test for muscarine-poisoning in

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[1] *Pouchet* fed dogs for months on these fungi, thus rendered innocuous, and they flourished upon them ; but dogs which had drunk the water in which the fungi had been expressed, all died in twenty-four to thirty-six hours. Indeed, *Gérard* himself and his family partook of fungi thus treated, without the slightest ill consequence. Taylor's work on Poisons, published by Seydeler. Cöln. 1863. III. Vol. p. 263.

criminal cases, in addition to the botanical test furnished by the remains of the fungi which may be found in the stomach and the intestinal canal, the so-called physiological test must be used as the most decisive.

In many cases the common unchanged urine applied directly to the frog's heart will be sufficient to arrest it immediately in diastole ; but the effect will be more surely produced by concentrated urine.

Sometimes it may be desirable to make an extract of the remains of the fungi found in the stomach and intestinal canal, or in the vomited matters and the fæces, and with this extract to make the experiment on the frog's heart. It is easily shown that the cessation of cardiac contraction thus produced does not depend on paralysis, because the heart responds to mechanical or electrical irritation by several rhythmic contractions, and pulsation may be restored by small doses of atropine.

Poisoning by Amanita Phalloides s. Venenosa.

Agaricus Bulbosus s. Viridis.

The cap (pileus) of this fungus is either quite white, or the white has a mixture of yellow or green ; the rim is white, unfurrowed ; the lamellæ are white ; the stem is knobby low down ; the flesh always white ; it is found during the whole summer in lightly wooded places. To its varieties belong Agaricus citrinus, virescens, and Hypophyllum albocitrinum (Husemann).

Etiology.

Cases of poisoning by these fungi are rather frequent, and generally proceed from ignorance of their poisonous character, or from mistaking them for edible mushrooms. Reports of such cases are numerous both in ancient and in modern times. Amanita bulbosa and its varieties produce some of the most dangerous of

fungus poisonings. We have not yet succeeded in ascertaining accurately the active principle of this fungus, though great efforts have been made to discover it. Sicard and Schoras [1] first expressed the opinion that the active constituents of poisonous fungi were bases; then Letellier and Speneux [2] obtained an acrid, fixed poison, which acted violently on the stomach and the intestinal canal, and also a second poison which they called amanitin, and which affected the nerves. This amanitin was a brownish, non-crystalline, readily soluble substance, devoid of taste and odor; when treated with acids, it became partially converted into sugar, like the glucosides. These two poisonous bodies could not be obtained pure, but consisted of a mixture of several substances. E. Boudier [3] obtained an alkaline body out of Amanita bulbosa, which he called bulbosine; it is distinguished from muscarine by a sharp, bitter taste, yet it strikingly resembles muscarine in its behavior as to solubility, so that Schmiedeberg considers bulbosine to be identical with muscarine. For Boudier's bulbosine is readily soluble in water and absolute alcohol, insoluble or very sparingly soluble in ether and chloroform, like muscarine. Still, notwithstanding the probability of Schmiedeberg's view, no absolute confirmation of it as yet exists.

Pathology.

Symptoms and Course.

It is clearly ascertained from numerous reports founded on experience, that poisoning by Amanita phalloides and its varieties produces two groups of symptoms: one affecting the intestinal region, the other the nervous system. It may happen, from various accidental causes, that sometimes one group of symptoms is more prominent, sometimes the other, but in general they are fairly balanced. The following cases may illustrate all

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[1] Journ. de Pharmaz. et de Chim. Juin. 1865.

[2] Annal. d'Hyg. publique. Janvier. p. 71. 1867.

[3] Des Champignons, etc. Paris. 1866.

that we know at present respecting this poison. In one case[1] the poisoning was of the gastro-intestinal type. A woman and her daughter were simultaneously poisoned; they were attacked with violent gastric pains and choleraic symptoms, to which the mother succumbed after fifty-two, the daughter after sixty hours. Goudot[2] relates a case in which seven persons were poisoned by Hypophillum albocitrinicum. The symptoms appeared at the earliest twelve hours, at the latest twenty-nine hours after the introduction of the fungi. In the slighter cases the symptoms were diarrhœa and vomiting, with excessive thirst and sural cramps; the consciousness remained undisturbed. In the severe cases vomiting, colic, diarrhœa, and convulsions appeared, with dejection, anxiety, slow and feeble pulse, which sank to fifty-six beats. Towards the approach of death, which did not supervene till after forty-eight or seventy-two hours, in one case seven days, after the poison had been introduced, general convulsions, trismus, loss of consciousness, and tetanus set in. In some cases, described by Maschka,[3] in addition to violent gastro-intestinal symptoms, general and partial convulsions, fainting, giddiness, delirium, somnolence, coma, etc., were observed. Taylor[4] describes a case of poisoning by Amanita citrina; a child died in convulsions on the second day, the mother died on the fifth day, with vomiting, diarrhœa, general insensibility and stupor. Ollivier[5] relates of a physician at Batna (Algiers), that he and his family partook of mushrooms which had grown on a dunghill, which, however, were really Amanita bulbosa. The symptoms appeared about six hours after the meal, and fourteen hours after the first vomiting death supervened with marked cyanosis and tetanus. Carragon[6] reports the fatal poisoning of five French soldiers at Laon, who had partaken of a dish of mushrooms,

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[1] Empoisonnement par les Champignons. Journ. de Chim. méd. p. 713. 1846.

[2] Empoisonnement par les Champignons de sept personnes; dont quatre guérisons et trois morts à Cubzy-les-soing (Haute Saône). Union méd. No. 116. p. 466. 1852.

[3] Einiges über Vergiftung mit Schwämmen. Prager Vierteljahrschr. 1855. 2. Bd. p. 137.

[4] Guy's Hosp. Report. Vol. XI. 16. 1866.

[5] Journal de Chim. médic. 1868.

[6] Gaz. des Hôpit. 140. p. 1146. 1873.

really Amanita bulbosa. The symptoms of poisoning, which did not set in till eleven hours after the meal, were chiefly of a choleraic nature. Two died on the second day, two on the third, and one not till the fifth day.

As regards the results of autopsies, prognosis, diagnosis, treatment and test of the poisoning, what has been said of muscarine-poisoning holds good generally for poisoning by Amanita phalloides and its varieties. We have only a few reports by Letellier and Speneux[1] of their experiments on animals; these were performed with the mixture which they obtained and called amanitine.

Doses of a grain and a half (0.1) of Letellier's amanitin act poisonously upon frogs in ten to thirty minutes; with rabbits doses of fifteen grains (1.0) are necessary to produce torpor, stupor, reduction of frequency of respiration, paralytic symptoms, coma, and finally death preceded by slight convulsions.

When smaller doses are administered, recovery may set in after five to six hours. Cats are more sensitive than rabbits to this poison; this circumstance is in favor of the supposed identity between muscarine and the poisonous factor present in Amanita phalloide-

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Poisoning with Russula Integra and Boletus Luridus.

Russula integra (Agaricus integer, Agaricus emeticus) has stiff lamellæ; is sapless, brittle, and of different colors—red, brown, violet, white, yellow, etc. Poisoning by means of this fungus was very frequent in former times; recently it has become extremely rare. The effect of it is a complication of strongly marked choleraic symptoms, which very soon terminate fatally. The result of autopsies corresponds to the clinical symptoms, which of themselves indicate the treatment. We have no accurate knowledge of the active constituent of the Russula integra; but we may conclude, from the fact that long cooking renders this fungus innocuous, whereas a rapid culinary process, such as

[1] Annal. d'Hygiène publ. Janvier. 1867.

roasting, etc., fails to deprive it of its poisonous properties, that the poisonous factor is volatilized by the higher temperature.

Boletus luridus (Boletus perniciosus, B. bovinus) has an olive green or brown cap (pileus), a firm, knobby, red stem; it grows in summer and autumn in pine and other woods; the flesh of the cap is white or yellowish; when broken up it changes into dark blue (Husemann).

This fungus also produces violent gastric and intestinal symptoms—vomiting, diarrhœa, severe colicky pains, collapse, and convulsions—and the result is often fatal. Almén[1] has obtained from Boletus luridus a substance which is apparently an alkaloid, and forms a precipitate with tannin. If this supposed alkaloid is really the poisonous principle of the boletus, its behavior toward tannin would be valuable in the treatment of this poisoning. In treating it, we must first endeavor to procure the elimination of the fungus from the intestinal canal, then attend to the collapse, respiratory and cardiac action, and also seek to relieve the subjective sufferings of the patient by administering opiates, etc.

The symptoms produced by these fungi are very much the same as those which follow poisonings by the other varieties, so that what has been said above may be easily applied to the possible action of other fungi.

Poisoning with the Lower Forms of Fungi.

Partly for the sake of completeness, partly because poisoning with the lower forms of fungi may be regarded as a sort of transition from intoxications, properly so called, to infectious diseases, which are nowadays generally attributed to small fungi, we may be allowed to devote a few words to cases of poisoning by the lower fungi.

A frequent phenomenon in our ordinary victuals is the formation of mouldy fungi. Although it is a fact that human

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[1] Upsala Läkareforenings Förhandl. Bd. II. H. 4. p. 274. 1868.

beings may consume great quantities of such mouldy fungi without the slightest injury, yet examples are not wanting to prove that very violent attacks of illness, even death, may be the result of eating decayed food of this kind. Thus we have a recent account[1] of the poisoning of a family of three persons by eating mouldy bread; they all suffered from colic, vomiting, and very violent convulsions. The adults recovered, but a little girl, five years of age, died of this poisoning.

Boudier[2] relates a similar case of a woman who, with her two children, had eaten cherries tainted by Vert-de-gris (Cladosporium herbarum). They became seriously ill, had violent gastric and intestinal pains, attacks of colic, vomiting, copious watery evacuations, coldness of the extremities, but recovered through the administration of opium and stimulants.

These cases of poisoning closely resemble those produced by decayed mushrooms, and it is possible that, in the latter case, more weight ought to be attached to the decomposition of the food than to the actual fungi.

Kennedy[3] communicates a remarkable case. A boy threw mouldy linseed in his schoolfellow's face with such violence that some of the seeds made their way into his eyes, his mouth, and even his larynx. He was attacked with severe pain, watering of the eyes, sneezing, coughing, dyspnœa, œdema of the face and eyelids. The next day fever set in, and an exanthem resembling measles, which soon disappeared, but the bronchitis and dyspnœa lasted for some time. It is very probable that it was the fungi which kept up the last symptoms so long.

Till quite recently so-called hay fever or hay asthma, also called summer catarrh, was regarded as a pendant to the above-mentioned symptoms produced by the action of lower fungi, as a fungus was supposed to be the cause of this distressing catarrh, which often attacks people at the period of the ripening of meadow-grass and of the hay harvest. In support of the theory that fungi were the real cause of this malady, the case of Helmholtz

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[1] Pharmazeut. Zeitschrift für Russland. 1866. p. 572.

[2] Des Champignons, etc. Paris. 1866.

[3] Dubl. Quart. Journal. 1863. Feb.

was triumphantly cited. This distinguished scholar suffered long and repeatedly from hay fever, which usually attacks the same people every summer. Professor Binz, of Bonn, treated Helmholtz with local application of solution of quinine, and the symptoms of catarrh were ameliorated in a very short time, although a considerable time elapsed before complete recovery set in.

Recently, however, we have been enlightened as to the true cause of hay fever, especially by the admirable treatise of Charles H. Blackley,[1] who proved experimentally that the causa noxia was not a fungus, but certain pollen proceeding from various grasses, and which, when breathed in by persons unaccustomed to the open air, produces the symptoms of hay fever. When this pollen reaches the mucous membrane of the respiratory organs, it swells up, discharges its granular contents through the burst membrane, whereupon the liberated granula, by their lively movement, may produce catarrh. It is not yet decided whether some chemical irritation as yet unknown is at work or not, but it is very probable, as we know no analogous instance of the maintenance of such persistent inflammatory symptoms, by a simple fine powdery organic substance. Hitherto we have no data whatever for fixing upon this supposed chemical substance. Hay fever affords an example of the close connection between poisoning and infectious diseases. For further details concerning hay fever, see Zuelzer's treatise upon it in this manual (Vol. II.).

Dr. Miquel[2] reports a similar form of disease produced by fungi (stilbosporei ?), a dust-like fungus, with poisonous action, which is developed on the old stem of Arundo donax. Peasants defend themselves against this dust by veiling their faces. If the fungus settles upon human beings, after twenty-four hours fever is set up, with gastric pains, weight and giddiness in the head, heat and burning in the face, upon which an exanthem appears in the form of vesicles and pustules. If the dust penetrates into the air-passages, violent coughing and dyspnœa ensue ; if it enters the intestinal canal it produces colic, vomiting, and diar-

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[1] Experimental Researches on the Causes and Nature of Catarrhus Æstivus (Hay Fever, Hay Asthma). London. 1873.

[2] Note sur une maladie non encore décrite, communiquée à l'homme par la Canne de Province. Bullet. général de thérap., méd., et chirurg. Juin. 1845.

rhœa. The genitals also swell and become painful, so that satyriasis and symptoms of nymphomania may be developed. Miquel relates four of these cases: one was that of a man sixty-one years of age, in whom the inflammation of the skin turned to gangrene, which put an end to his life. In general, the symptoms soon disappear, and, with peeling of the skin, recovery sets in. Warm baths, oleaginous friction, laudanum, and cooling beverages proved to be beneficial and effectual in the other cases.

Whether the symptoms in this disease are produced by an actual poison attaching to the fungus, or whether its form may not be the cause of the inflammatory processes, as in the case of the hair of certain caterpillars, *e. g.*, the bear-worm, etc., is not yet ascertained ; we incline to the latter view.

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